Chapter 4
The Health Benefits of Smoking Cessation

Introduction

Evidence on the health benefits of smoking cessation continues to expand and evolve since the topic was last covered comprehensively in the 1990 report of the Surgeon General. This chapter primarily reviews the findings published between 2000 and 2017 on disease risks from smoking and how these risks change after smoking cessation for major types of chronic diseases, including cancer, the cardiovascular and respiratory systems, and a wide range of reproductive outcomes. The more recent studies expand the observational evidence documenting the benefits of smoking cessation and provide insights into the mechanisms underlying these benefits. The review of the effects of smoking cessation on reproductive outcomes documents health benefits of maternal smoking cessation across all phases of reproduction, from preconception to birth, and also for male reproductive health. Chapter 5 summarizes the health benefits of smoking cessation for all-cause mortality in the general population; thus, that topic is not discussed here.

This chapter also addresses the clinically relevant benefits of cessation for mitigating the effects of diseases, particularly in persons with cancer and coronary heart disease. This general topic received mention in previous Surgeon General's reports (U.S. Department of Health and Human Services [USDHHS] 1982, 1983, 1990, 2004), and the consequences of smoking following a diagnosis of cancer received specific attention in the 2014 Surgeon General's report, leading to a conclusion that cigarette smoking has adverse causal effects on persons already diagnosed with cancer (USDHHS 2014). This chapter also reviews cessation and cardiovascular disease and the implications of cessation for the natural history of chronic obstructive pulmonary disease.

Methodologic Challenges

There are methodologic challenges related to assessing smoking cessation and its links to health outcomes in both observational and intervention studies. Risks in former smokers should be compared with those of current or never smokers, thus necessitating a precise definition of former smoking (Lindstrom 2010); the same is true for time since cessation, cumulative smoking (e.g., pack-years [which is defined as the number of packs of cigarettes smoked per day multiplied by the number of years smoked], which incorporates both smoking intensity and duration), and changes in smoking status during follow-up.

Observational studies should consider factors that might differ between those who quit smoking and those who continue to smoke. Some persons may quit smoking because they are sick, and health-conscious persons may be more motivated to quit. In an effort to address bias attributable to "sick quitters," those with preexisting diseases can be excluded from analyses. This strategy also addresses "reverse causation," or quitting because of the development of symptoms or a disease. Whenever possible, observational analyses should also adjust for other risk factors that may confound the relationship between smoking habits and disease risk.

Cancer

This section reviews evidence from epidemiologic studies about the impact of smoking cessation on the risk of 12 cancers caused by smoking, as concluded in previous Surgeon General's reports (U.S. Department of Health and Human Services [USDHHS] 2004, 2014). The types of cancers reviewed for this section include cancers of the lung, larynx, oral cavity and pharynx, esophagus, pancreas, bladder, stomach, liver, colon and rectum, kidney, and cervix and acute myeloid leukemia (AML).

Conclusions from Previous Surgeon General's Reports

At the time of release of the 1990 Surgeon General's report, the U.S. Surgeon General and/or the International Agency for Research on Cancer (IARC) classified six cancers as causally associated with cigarette smoking: cancer of the lung, larynx, oral cavity and pharynx, esophagus, pancreas, and bladder (USDHHS 1990). The 1990 Surgeon

General's report concluded that smoking cessation reduced the risk of these six cancers. That report set forth nine conclusions about smoking cessation and cancer (Table 4.1). The 2004 and 2014 Surgeon General's reports concluded that smoking causes at least six additional cancers beyond those for which the associations were considered causal in 1990: cancer of the stomach, liver, colon and rectum, kidney, cervix, and AML (USDHHS 2004, 2014). However, the 2004 and 2014 Surgeon General's reports did not explicitly conclude that smoking cessation reduces the risk of these six additional cancers.

Biological Mechanisms

Smoking contributes to carcinogenesis through multiple biological mechanisms, including direct genotoxicity, hypermethylation of gene promoters, receptor-mediated pathways, and inflammation (USDHHS 2010, 2014; Hecht 2012). In addition, smoking has been shown to increase the somatic mutation load (Alexandrov et al. 2016). Collectively, these mechanisms can act at the early and late stages of carcinogenesis, implying that smoking cessation could have short- and long-term effects on the risk of cancer. Regardless of the specific mechanisms, smoking cessation ends further increments to cumulative exposure to tobacco smoke and, therefore, is expected to reduce the risk of cancers caused by smoking, since cumulative exposure does not increase further, allowing repair processes to come into play (USDHHS 2010). The particular mechanisms that are most important in smoking-induced carcinogenesis likely vary by site, as described below.

Literature Review Methods

For this report, systematic literature reviews were not conducted for the six cancers (lung, larynx, oral cavity and pharynx, esophagus, pancreas, and bladder) for which the 1990 Surgeon General's report (USDHHS 1990) concluded that smoking cessation reduces risk. Instead, for these sites, this report summarizes new evidence from large pooled analyses or meta-analyses that were determined to clarify the consequences of smoking cessation.

For the six smoking-attributable cancer sites for which smoking cessation has not previously been concluded to lower risk (stomach, liver, colon and rectum, kidney, cervix, and AML), epidemiologic evidence was reviewed in great detail (USDHHS 1990, 2004, 2014). The evidence review focused on whether relative risks (RRs) (a) are lower for former smokers than for current smokers and (b) decrease in former smokers with increasing number of years since cessation. Summary RRs for former and current smokers of cigarettes, compared with never smokers, were identified from the most recent sufficiently comprehensive meta-analyses, as found through literature searches conducted in January 2017 of the National Library of Medicine's PubMed service. For some papers, current cigarette smokers were the comparison group for former smokers.

Table 4.1 Conclusions from the 1990 Surgeon General's report on the health benefits of smoking cessation and cancer

Conclusions
1. Smoking cessation reduces the risk of lung cancer compared with continued smoking. For example, after 10 years of abstinence, the risk of lung cancer is about 30 to 50 percent of the risk for continuing smokers: with further abstinence, the risk continues to decline.
2. The reduced risk of lung cancer among former smokers is observed in males and females, in smokers of filter and nonfilter cigarettes, and for all histologic types of lung cancer.
3. Smoking cessation lowers the risk of laryngeal cancer compared with continued smoking.
4. Smoking cessation reduces the severity and extent of premalignant histologic changes in the epithelium of the larynx and lung.
5. Smoking cessation halves the risks for cancers of the oral cavity and esophagus, compared with continued smoking, as soon as 5 years after cessation, with further reduction over a longer period of abstinence.
6. Smoking cessation reduces the risk of pancreatic cancer, compared with continued smoking, although this reduction in risk may only be measurable after 10 years of abstinence.
7. Smoking is a cause of bladder cancer; cessation reduces risk by about 50 percent after only a few years, in comparison with continued smoking.
8. The risk of cervical cancer is substantially lower among former smokers in comparison with continuing smokers, even in the first few years after cessation. This finding supports the hypothesis that cigarette smoking is a contributing cause of cervical cancer.
9. Neither smoking nor smoking cessation are associated with the risk of cancer of the breast.

Source: U.S. Department of Health and Human Services (1990, p. 10).

The literature searches for the six sites for which smoking cessation has not been previously tied to risk at the casual level used the term "smoking or tobacco," a term for the specific cancer of interest (e.g., "colorectal neoplasms" or "liver neoplasms"), and limited the publication types to "meta-analysis." The same terms were used in literature searches of PubMed to identify, for each cancer, individual studies published after the time period covered by the most recent comprehensive meta-analysis. All studies identified through meta-analyses or literature searches were examined to determine whether they included results by the number of years since cessation. Results by years since cessation were tabulated in summary tables. Because there were many studies of cessation in relation to stomach and colorectal cancer, summary tables for these cancers include only results from cohort studies, which generally have less potential for bias than case-control studies.

Epidemiologic Evidence

Cancers for Which Previous Surgeon General's Reports Have Concluded That Smoking Cessation Reduces Risk

Lung

The 2004 Surgeon General's report added to the conclusions of the 1990 Surgeon General's report by noting that, while the risk of lung cancer declines with increasing numbers of years since cessation, the risk remains higher in former smokers than in never smokers, even after many years of not smoking (USDHHS 2004). The 2014 Surgeon General's report covered findings from more recent reports documenting a rise of RR in smokers (USDHHS 2014). For this report, epidemiologic studies of smoking cessation and risk of lung cancer were reviewed in detail in publications by IARC, including two monographs (International Agency for Research on Cancer 2004, 2012) and a cancer prevention handbook that focused specifically on the effects of smoking cessation (IARC 2007). In the handbook, IARC (2007) included meta-analyses with separate estimates of summary RRs for smoking cessation grouped by gender and global region. In most groups, estimates of summary RRs for former smokers were about 0.7–0.8 compared with continuing current smokers up to 10 years after cessation, about 0.3 from 10 to 19 years after cessation, and even lower with longer periods of successful quitting.

There is an ongoing need to examine the relationship between smoking cessation and lung cancer for the following reasons: (a) In the United States, lung cancer due to smoking still accounts for the majority of lung cancer deaths (U.S. Cancer Statistics Working Group 2019), and (b) changes have occurred over time in the epidemiologic relationship between smoking and lung cancer (USDHHS 2014). This report includes data from three large U.S. cohorts: the Cancer Prevention Study-II (CPS-II) (lung cancer mortality follow-up, 1982–1988) and two cohorts with follow-up for the incidence of lung cancer from the 1990s and 2000s—the CPS-II Nutrition Cohort (Calle et al. 2002) and the Prostate, Lung, Colorectal, and Ovarian cancer screening cohort (PLCO) (Pinsky et al. 2015) (Figure 4.1). The American Cancer Society provided, specifically for this report, analyses of the CPS-II cohort and CPS-II Nutrition Cohort. RRs by the number of years since cessation, analyzed as a time-varying variable in 5-year categories, were similar in the three cohorts (Figure 4.1, Table 4.2). As shown, a former cigarette smoker's risk of lung cancer decreases to half that of a similarly aged continuing smoker about 10–15 years after cessation. RRs continue to decline as time since cessation increases, but RRs remain higher in former smokers than in persons who have never smoked (Table 4.2). Results by histologic subtype from the PLCO cohort suggest that RRs may decline somewhat more slowly for adenocarcinoma than for squamous cell carcinoma (Pinsky et al. 2015). Table 4.3 provides results using never cigarette smokers as the reference group rather than current smokers.

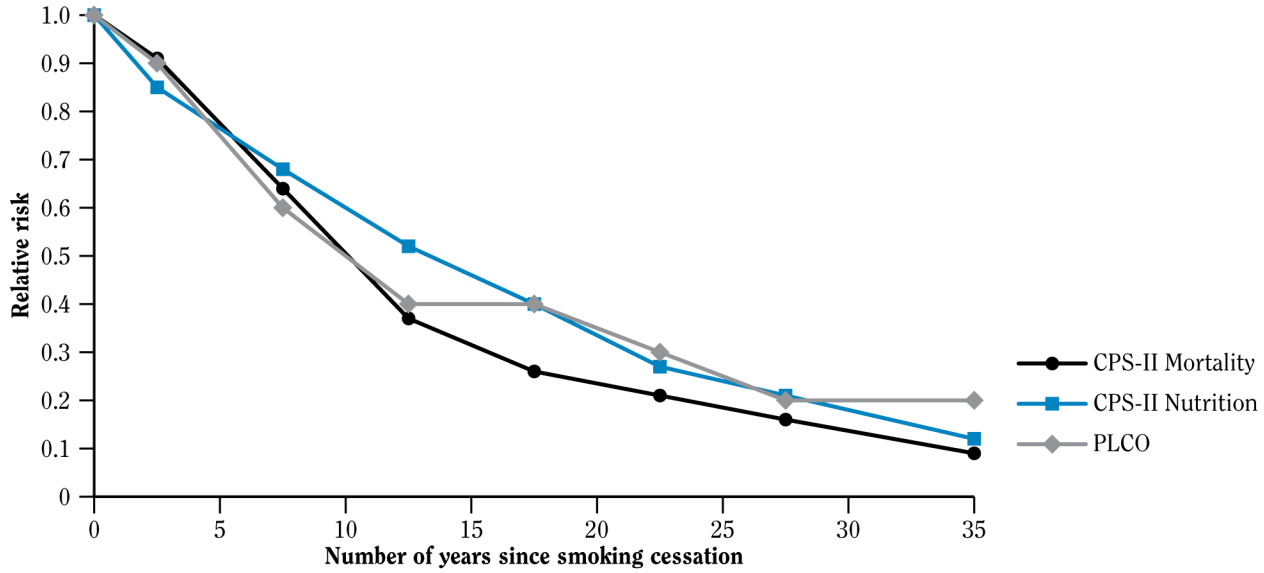
A few studies that examined age at smoking cessation, rather than number of years since cessation, consistently showed that compared with continued smoking, the earlier the age at quitting, the lower the risk of lung cancer (International Agency for Research on Cancer 2004) (Peto et al. 2000; Jha et al. 2013; Pirie et al. 2013; Thun et al. 2013a). Notably, results of these studies indicate that quitting smoking by age 40, rather than continuing to smoke, will eliminate most of the excess risk of developing lung cancer faced by long-term smokers later in life.

Since the 1990 Surgeon General's report, substantial research has addressed the genetic determinants of risk for lung cancer among cigarette smokers (Chen et al. 2016; Liu et al. 2017). Genetic variation in the α5 nicotinic cholinergic receptor subunit *(CHRNA5)* has been linked to risk for lung cancer, as low- and high-risk genotypes have been identified. Chen and colleagues (2016), who carried out a meta-analysis involving cohort and case-control studies from two collaborative groups, found that the number of years by which a diagnosis of lung cancer was delayed following cessation was the same for the two genotypes.

Larynx, Oral Cavity, and Pharynx

Previous Surgeon General's reports have concluded that smoking is a cause of laryngeal cancer (U.S. Department of Health, Education, and Welfare [USDHEW]

Figure 4.1 Relative risk of lung cancer incidence or mortality by number of years since smoking cessation, compared with continued smoking, in three large U.S. cohorts



Source: American Cancer Society, unpublished data.
Note: **CPS =** Cancer Prevention Study; **PLCO =** Prostate, Lung, Colorectal, and Ovarian cancer screening cohort.

1964), cancer of the oral cavity (USDHEW 1979b), and cancers of the oral cavity and pharynx (USDHHS 2004). The 1990 Surgeon General's report concluded that "smoking cessation lowers the risk of laryngeal cancer compared with continued smoking [and] . . . halves the risk for cancer of the oral cavity and esophagus . . . as soon as 5 years after cessation" (USDHHS 1990, p. 10).

Results of studies published since the 1990 Surgeon General's report (IARC 2004, 2012; Marron et al. 2010) have strengthened the evidence that risks of both laryngeal cancer and cancer of the oral cavity and pharynx are approximately halved within 10 years of cessation. Further, the International Head and Neck Cancer Epidemiology Consortium, which conducted a very large pooled analysis of data on smoking cessation from 17 case-control studies (Marron et al. 2010) that included a total of 12,040 cases and 16,884 controls, found gradients of declining RR with increasing numbers of years since cessation. The findings were similar for cancers of the larynx, oral cavity, and pharynx. Compared with continued cigarette smokers, reductions in RR in former smokers were approximately 30% within 5 years of cessation, 50% from 5 to 9 years after cessation, and 80% 20 or more years after cessation. These estimates for RR may actually underestimate the decline in this measure resulting from smoking cessation because they were adjusted for pack-years of smoking (USDHHS 1990).

Esophagus

The 1979 Surgeon General's report concluded that smoking is a cause of esophageal cancer (USDHEW 1979b), and the 1990 Surgeon General's report concluded that smoking cessation halves the risk of esophageal cancer as soon as 5 years after cessation (USDHHS 1990). In addition, the 2004 Surgeon General's report concluded that smoking causes squamous cell carcinoma of the esophagus, historically the predominant histologic type of cancer at this site, as well as adenocarcinoma (USDHHS 2004), which is currently the most common type of esophageal cancer in the United States (Hur et al. 2013; Xie et al. 2017). Studies of esophageal squamous cell carcinoma have revealed declining risks with increasing number of years since cessation among former smokers (IARC 2004, 2007, 2012), and most studies of esophageal adenocarcinoma have also found lower risk in former cigarette smokers than in current smokers (IARC 2012). Notably, a large pooled analysis of esophageal adenocarcinoma and esophageal gastric junction adenocarcinoma from 11 studies, including 10 case-control studies and 1 cohort study, found an approximate 30% reduction in relative risk among former cigarette smokers who had quit for at least 10 years compared with continuing smokers, even after adjusting for pack-years of smoking (Cook et al. 2010).

Table 4.2 Relative risk of lung cancer incidence or mortality by number of years since smoking cessation, compared with continued smoking, in three large U.S. cohorts

	CPS-II 1982–1988 (mortality)[a]		CPS-II Nutrition Cohort 1992–2011 (incidence)[b]		PLCO 1993–2009 (incidence)[c]	
	Deaths	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Current smokers	2,571	1.00 (referent)	880	1.00 (referent)	271	1.00 (referent)
Never smokers	332	0.05 (0.046–0.059)	358	0.04 (0.035–0.045)	253	0.03 (0.02–0.03)
Former smokers, by number of years since smoking cessation	—	—	—	—	—	—
≤5	193	0.91 (0.78–1.06)	293	0.85 (0.74–0.97)	83	0.86 (0.67–1.10)
>5–10	360	0.64 (0.57–0.72)	411	0.68 (0.60–0.74)	90	0.62 (0.48–0.78)
>10–15	220	0.37 (0.32–0.42)	400	0.52 (0.46–0.58)	151	0.41 (0.33–0.51)
>15–20	179	0.26 (0.22–0.30)	361	0.40 (0.35–0.45)	236	0.38 (0.30–0.47)
>20–25	137	0.21 (0.18–0.25)	277	0.27 (0.24–0.31)	173	0.28 (0.22–0.35)
>25–30	82	0.16 (0.13–0.20)	241	0.21 (0.18–0.24)	101	0.23 (0.17–0.30)
>30	97	0.09 (0.07–0.11)	648	0.12 (0.11–0.13)	111	0.18 (0.14–0.23)

Source: American Cancer Society, unpublished data.
Notes: **CI =** confidence interval; **CPS =** Cancer Prevention Study; **PLCO =** Prostate, Lung, Colorectal, and Ovarian cancer screening cohort; **RR =** relative risk.
[a]Analyses of the CPS-II mortality cohort were restricted to those 55 years of age and older and excluded ever pipe/cigar smokers, those with prevalent cancer, and those with unknown smoking status. Data were adjusted for race, sex, and level of education.
[b]Analyses of the CPS-II Nutrition Cohort were restricted to those 55 years of age and older and excluded those with prevalent cancer. Data were adjusted for race, sex, and level of education.
[c]Analyses of participants in the PLCO were restricted to those 55 years of age and older and excluded ever smokers with more than 30 pack-years of cigarette smoking. RRs provided in the published analysis (Pinsky et al. 2015) used never smokers as the referent group. Using current smokers as the referent group, Paul Pinsky, Ph.D., of the National Cancer Institute provided equivalent results for this report.

Pancreas

The 1990 Surgeon General's report concluded that smoking cessation reduces the risk of pancreatic cancer, but noted that "this reduction in risk may only be measurable after 10 years of abstinence" (USDHHS 1990, p. 10). In a meta-analysis performed by Iodice and colleagues (2008) of 14 studies with analyses by number of years since cessation, the summary RRs, compared with never smokers, were 1.74 (95% confidence interval [CI], 1.61–1.87) for current cigarette smokers, 1.48 (95% CI, 1.25–1.76) for persons with less than 10 years since smoking cessation, 1.15 for persons with 10 or more years since cessation, and 0.95 for persons with 20 or more years since cessation. In other large pooled analyses of cohort studies (Lynch et al. 2009) and case-control studies (Bosetti et al. 2012), RRs declined with increased time since cessation, and no excess risk (compared with never smokers) was observed among former smokers with 20 or more years since quitting (Bosetti et al. 2012). Thus, collectively, the available scientific evidence indicates that the RR for pancreatic cancer declines steadily with increased time since cessation and approaches that of never smokers approximately 20 years after quitting smoking.

Bladder

The 1990 Surgeon General's report concluded that "[smoking] cessation reduces risk [of bladder cancer] by about 50 percent after only a few years in comparison with continued smoking" (USDHHS 1990, p. 10). Since that report, many studies have provided more evidence that RRs for bladder cancer are lower in former cigarette smokers than in current smokers and that they decline steadily as the number of years since cessation increases (IARC 2004, 2012; Freedman et al. 2011; Jiang et al. 2012). In comparisons with continued smoking, most studies have observed measurable reductions in risk for bladder cancer within 10 years of smoking cessation. In the three largest studies (Hartge et al. 1987; Brennan et al. 2000; Freedman et al. 2011), however, each of which included more than 2,500 cases of bladder cancer in their

Table 4.3 Relative risk of lung cancer incidence or mortality by number of years since smoking cessation, compared with never smokers, in three large U.S. cohorts

	CPS-II 1982–1988 (mortality)[a]		CPS-II Nutrition Cohort 1992–2011 (incidence)[b]		PLCO 1993–2009 (incidence)[c]	
	Deaths	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Never smokers	332	1.00 (referent)	358	1.00 (referent)	253	1.00 (referent)
Current smokers	2,571	19.21 (17.09–21.59)	880	24.96 (22.02–28.28)	271	35.9 (29.0–44.5)
Former smokers, by number of years since smoking cessation	—	—	—	—	—	—
≤5	193	17.48 (14.58–20.96)	293	21.08 (18.03–24.64)	83	30.8 (23.4–40.5)
>5–10	360	12.30 (10.57–14.32)	411	16.96 (14.69–19.56)	90	22.1 (16.9–28.9)
>10–15	220	7.08 (5.96–8.41)	400	12.94 (11.20–14.94)	151	14.8 (11.9–18.2)
>15–20	179	4.93 (4.10–5.92)	361	9.90 (8.54–11.47)	236	13.5 (11.3–16.2)
>20–25	137	4.02 (3.29–4.92)	277	6.73 (5.75–7.88)	173	9.9 (8.1–12.0)
>25–30	82	3.13 (2.46–3.99)	241	5.21 (4.42–6.14)	101	8.1 (6.4–10.2)
>30	97	1.65 (1.32–2.07)	648	2.90 (2.55–3.31)	111	6.4 (5.1–8.0)

Source: American Cancer Society, unpublished data.
Notes: **CI =** confidence interval; **CPS =** cohort; **RR =** relative risk.
[a]Analyses of the CPS-II mortality cohort were restricted to those 55 years of age and older and excluded ever pipe/cigar smokers, those with prevalent cancer, and those with unknown smoking status. Data were adjusted for race, sex, and level of education.
[b]Analyses of the CPS-II Nutrition Cohort were restricted to those 55 years of age and older and excluded those with prevalent cancer. Data were adjusted for race, sex, and level of education.
[c]Analyses of participants in the PLCO were restricted to those 55 years of age and older and excluded ever smokers with more than 30 pack-years of cigarette smoking. RRs provided in the published analysis (Pinsky et al. 2015) used never smokers as the referent group. Using current smokers as the referent group, Paul Pinsky, Ph.D., of the National Cancer Institute provided equivalent results for this report.

analyses, more than 10 years since cessation was required before risk fell in former cigarette smokers to half that of continuing smokers.

Cancers for Which Previous Reports Have Not Concluded That Smoking Cessation Reduces Risk

Stomach

The 2004 Surgeon General's report concluded that there was sufficient evidence to infer a causal relationship between smoking and stomach cancer (USDHHS 2004). The association between smoking and this type of cancer is independent of *Helicobacter pylori* infection, an established risk factor for stomach cancer (Moy et al. 2010; IARC 2012). Potential biological mechanisms include chronic inflammation in the stomach and exposure to carcinogens in tobacco smoke, including tobacco-specific nitrosamines (Li et al. 2014).

A meta-analysis of more than 30 studies of cigarette smoking and risk for stomach cancer published through 2003 (Gandini et al. 2008) found that risk was lower for former cigarette smokers (RR = 1.31; 95% CI, 1.17–1.46) than for current smokers (RR = 1.64; 95% CI, 1.37–1.95) when compared with never smokers. Similar results were reported in studies published in 2003 or later (Gonzalez et al. 2003; Jee et al. 2004; Koizumi et al. 2004; Wen et al. 2004; Doll et al. 2005; Fujino et al. 2005; Lindblad et al. 2005; Sauvaget et al. 2005; Tran et al. 2005; Kurosawa et al. 2006; Freedman et al. 2007; Kim et al. 2007; Ozasa 2007; Sjodahl et al. 2007; Sung et al. 2007; Batty et al. 2008; Shikata et al. 2008; Zendehdel et al. 2008; Moy et al. 2010; Steevens et al. 2010; Nomura et al. 2012; Blakely et al. 2013; Tabuchi et al. 2013; Buckland et al. 2015; Chen et al. 2015; Eom et al. 2015; Jayalekshmi et al. 2015; Charvat et al. 2016).

Risk for stomach cancer by time elapsed since quitting among former cigarette smokers has been examined in nine cohort studies (Chao et al. 2002; Koizumi et al. 2004; Sauvaget et al. 2005; Freedman et al. 2007; Ozasa 2007; Zendehdel et al. 2008; Moy et al. 2010; Steevens et al. 2010; Ordonez-Mena et al. 2016). These studies are summarized in Table 4.4, but the table does not include studies that may underestimate the effect of smoking cessation (USDHHS 1990). For example, Table 4.4 does not include a small study from India that included many dual users

Table 4.4 Cohort studies of stomach cancer incidence or mortality, by number of years since smoking cessation

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Chao et al. (2002)	• Cohort study (Cancer Prevention Study II) • Men and women ≥30 years of age • 1,055,841 participants and 1,505 deaths from stomach cancer • United States • Follow-up period: 1982–1996	• Men: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 2.16 (1.75–2.67) ○ Former smoker: 1.55 (1.28–1.88) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ ≤10: 1.92 (1.50–2.47) ○ 11–19: 1.64 (1.26–2.14) ○ ≥20: 1.23 (0.95–1.59) – p for trend among former smokers: 0.0015 • Women – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.49 (1.18–1.88) ○ Former smoker: 1.36 (1.08–1.71) ○ Number of years since smoking cessation: – Never smoker: 1.00 (referent) ○ ≤10: 1.31 (0.91–1.87) ○ 11–19: 1.46 (1.00–2.13) ○ ≥20: 1.34 (0.95–1.89) – p trend among former smokers: 0.68	Adjusted for age; race; level of education; family history of stomach cancer; consumption of high-fiber grain foods, vegetables, and citrus fruits or juices; and use of vitamin C, multivitamins, and aspirin
Koizumi et al. (2004)	• Two population-based cohort studies • Men ≥40 years of age • Cohort 1: 9,980 men and 228 cases of stomach cancer • Cohort 2: 19,412 men and 223 cases of stomach cancer • Northern Japan • Follow-up period: – Cohort 1: 1984–1992 – Cohort 2: 1990–1997	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.84 (1.39–2.43) – Former smoker: 1.77 (1.29–2.43) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – <5: 1.72 (1.12–2.64) – 5–14: 2.08 (1.41–3.07) – ≥15: 1.31 (0.77–2.21)	Results from the two cohorts were pooled Adjusted for age, BMI, history of peptic ulcer, parental history of stomach cancer, type of health insurance, alcohol use, daily intake of pickled vegetables, and intake of bean-paste soup Cohort 1 also adjusted for intake of green or yellow vegetables and other vegetables and fruits Cohort 2 also adjusted for intake of spinach, carrots, pumpkin, cabbage, lettuce, Chinese cabbage, and oranges and other fruits

Table 4.4 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Sauvaget et al. (2005)	• Cohort study (Life Span Study) • 38,576 men and women who were in Hiroshima or Nagasaki (Japan) at the time of the atomic bombings in August 1945 • 1,280 cases of stomach cancer • Japan • Follow-up period: 1980–1999	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.50 (1.28–1.76) – Former smoker: 1.37 (1.13–1.66) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – 1–5: 1.29 (0.90–1.85) – 6–10: 1.32 (0.88–1.96) – 11–15: 1.06 (0.67–1.67) – ≥16: 0.74 (0.54–1.00)	Adjusted for city, sex, sex-specific age, calendar period, level of education, and radiation dose
Freedman et al. (2007)	• Cohort study (NIH-AARP Diet and Health Study) • 474,606 men and women ≥50 years of age who were members of AARP • 188 cases of stomach cardia and 187 cases of stomach non-cardia • Six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two U.S. metropolitan areas (Atlanta, Georgia; and Detroit, Michigan) • Follow-up period: 1995–2000	• Number of years since smoking cessation: – Cardia: • Never smoker: 1.00 (referent) • Current smoker: 2.87 (1.75–4.73) • 1–4: 2.39 (1.16–4.92) • 5–9: 2.73 (1.55–4.82) • ≥10: 2.01 (1.32–3.07) – Non-cardia: • Never smoker: 1.00 (referent) • Current smoker: 2.05 (1.33–3.18) • 1–4: 1.18 (0.54–2.62) • 5–9: 1.79 (1.05–3.05) • ≥10: 1.12 (0.78–1.63)	Adjusted for age, fruit intake, vegetable intake, total energy intake, sex, BMI, education level, alcohol intake, and physical activity Analyses of non-cardia cancer additionally adjusted for race/ethnicity

Table 4.4 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Ozasa (2007)	• Cohort study (Japan Collaborative Cohort Study for Evaluation of Cancer) • 1,048 deaths from stomach cancer • Japan • Follow-up period: starting in 1988	• Men: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.47 (1.19–1.80) ○ Former smoker: 1.22 (0.97–1.53) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ <5: 1.19 (0.84–1.67) ○ 5–14: 1.25 (0.94–1.67) ○ ≥15: 1.14 (0.84–1.55) • Women: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 0.86 (0.50–1.48) ○ Former smoker: 1.07 (0.50–2.28) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ <5: 0.61 (0.08–4.37) ○ 5–14: 1.35 (0.43–4.23) ○ ≥15: 0.56 (0.07–4.02)	Adjusted for age and area of study

Table 4.4 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Zendehdel et al. (2008)	• Cohort study • 336,381 men in the Swedish building industry who had records of at least one preventive health checkup between 1971 and 1993 • 276 cases of stomach cardia and 1,109 cases of stomach non-cardia • Nord-Trondelag County, Norway • Follow-up period: from date of initial checkup to 2004	• Cardia: – Smoking status: ○ Never smoker: 1.0 (referent) ○ Current smoker: 2.3 (1.6–3.3) ○ Former smoker: 1.8 (1.2–2.7) – Number of years since smoking cessation: ○ Never smoker: 1.0 (referent) ○ <5: 1.9 (1.1–3.4) ○ ≥5: 1.7 (1.1–2.6) – p trend among former smokers: 0.7 • Non-cardia: – Smoking status: ○ Never smoker: 1.0 (referent) ○ Current smoker: 1.4 (1.2–1.6) ○ Former smoker: 1.3 (1.1–1.5) – Number of years since smoking cessation: ○ Never smoker: 1.0 (referent) ○ <5: 1.2 (0.9–1.6) ○ ≥5: 1.3 (1.1–1.6) – p trend among former smokers: 0.6	Adjusted for age and BMI Definition of smoking included pipe/cigar smoking, but study population predominantly smoked cigarettes
Moy et al. (2010)	• Cohort study (Shanghai Cohort Study) • 18,244 men 45–64 years of age • 391 cases of stomach cancer • Shanghai, China • Follow-up period: 1986–2005	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.55 (1.23–1.96) – Former smoker: 1.79 (1.25–2.57) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – Current smoker: 1.30 (0.82–2.05) – <5: 1.24 (0.66–2.34) – 5–9: 0.91 (0.49–1.66) – ≥10: 0.64 (0.51–0.81)	Adjusted for age, year, and neighborhood

Table 4.4 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Steevens et al. (2010)	• Cohort study (Netherlands Cohort Study) • 120,852 men and women (3,962 in the subcohort for the case-cohort design) 55–70 years of age • 164 cases of cardia and 491 cases of non-cardia • The Netherlands • Follow-up period: 1986–2002	• Number of years since smoking cessation: – Cardia: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.61 (0.97–2.66) ○ <10: 1.72 (0.97–3.05) ○ 10–19: 1.43 (0.81–2.52) ○ ≥20: 1.00 (0.53–1.91) – Non-cardia: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.86 (1.39–2.47) ○ <10: 1.81 (1.30–2.52) ○ 10–19: 1.41 (0.98–2.02) ○ ≥20: 1.13 (0.77–1.67)	Cases in the case-cohort approach derived from entire cohort and number of person-years at risk for entire cohort estimated from a subcohort of 5,000 men and women who were randomly sampled from the total cohort at baseline Adjusted for age; sex; alcohol use; BMI; level of education; energy intake; and intake of fruits, vegetables, and fish
Ordonez-Mena et al. (2016)	• Collaboration of 19 prospective cohort studies • 897,021 men and women • 1,866 cases of stomach cancer and 1,396 deaths from stomach cancer • Europe and United States	• Incidence of stomach cancer: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.74 (1.50–2.02) ○ Former smoker: 1.18 (0.95–1.46) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ ≤9: 0.85 (0.60–1.20) ○ 10–19: 0.68 (0.41–1.12) ○ ≥20: 0.69 (0.51–0.93) – p trend among former smokers: 0.0461 • Death from stomach cancer: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.73 (1.36–2.19) ○ Former smoker: 1.31 (1.02–1.68) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ ≤9: 1.13 (0.80–1.58) ○ 10–19: 0.72 (0.46–1.14) ○ ≥20: 0.87 (0.64–1.19) – p trend among former smokers: 0.2355	Analyses of number of years since smoking cessation included only cohorts with these data and therefore included substantially fewer participants Adjusted for sex, age, BMI, level of education, vigorous physical activity, history of diabetes, and alcohol consumption

Notes: **AARP =** formerly American Association of Retired Persons; **BMI =** body mass index; **CI =** confidence interval; **NIH =** National Institutes of Health; **RR =** relative risk.
[a]Studies are of cancer incidence unless number of cancer deaths is identified.
[b]p trend values are shown only if described as being among former smokers.

of cigarettes and bidis (Jayalekshmi et al. 2015), a study in which the highest category of number of years since quitting was only ≥3 years (Guo et al. 1994), or studies where the number of years since quitting was adjusted for duration or pack-years of smoking (Gonzalez et al. 2003; Sjodahl et al. 2007; Nomura et al. 2012). In general, risk estimates for the highest category of number of years since cessation (ranging from >10 years to >20 years) were lower than those for categories with fewer numbers of years since cessation (Table 4.4).

Colon and Rectum

The 2014 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between cigarette smoking and colorectal cancer (USDHHS 2014). For example, Botteri and colleagues (2008), in a meta-analysis of 26 studies of the incidence of colorectal cancer published through 2008, reported RRs of 1.17 (95% CI, 1.11–1.22) for former cigarette smokers and 1.07 (95% CI, 0.99–1.16) for current smokers, both compared with never smokers. Although the excess risk of colorectal cancer associated with current smoking overall was relatively small in this meta-analysis, there were statistically significant trends for increasing risk with increasing years of smoking duration, number of cigarettes smoked per day, and number of pack-years. In studies of colorectal cancer mortality that were included in the meta-analysis, summary RRs were 1.28 (95% CI, 1.15–1.42) for current smokers based on 14 studies, and 1.23 (95% CI, 1.14–1.32) for former smokers based on 12 studies (Botteri et al. 2008). Since 2008, four cohort studies that each included more than 1,000 incident cases of colorectal cancer (Hannan et al. 2009; Limsui et al. 2010; Leufkens et al. 2011) or deaths (Parajuli et al. 2014) have been published that provide RRs for both current and former cigarette smokers. In general, the RRs for current smokers were above those for former smokers:

- 1.27 (95% CI, 1.06–1.52) for current smokers and 1.23 (95% CI, 1.23 1.11–1.36) for former smokers (Hannan et al. 2009);

- 1.22 (95% CI, 1.04–1.41) for current smokers and 1.18 (95% CI, 1.02–1.36) for former smokers (Limsui et al. 2010);

- 1.31 (95% CI, 1.06–1.64) and 1.25 (1.04–1.50) for current and former smokers, respectively, with proximal colon cancer; and 0.91 (95% CI, 0.73–1.14) and 1.13 (95% CI 0.95-1.36) for current and former smokers, respectively, with distal colon cancer (Leufkens et al. 2011); and

- 1.27 (95% CI, 1.10–1.46) and 1.20 (95% CI, 1.03–1.38) for current and former smokers, respectively, who were men; and 1.30 (95% CI, 1.12–1.52) and 1.08 (95% CI, 0.90–1.30) for current and former smokers, respectively, who were women (Parajuli et al. 2014).

Taken together, these four studies provide evidence that former smokers have somewhat lower risk for colorectal cancer than do current smokers. Twelve cohort studies have examined risk of colorectal cancer by time since cessation, as summarized in Table 4.5 (Chao et al. 2000; Rohan et al. 2000; Limburg et al. 2003; Ozasa 2007; Kenfield et al. 2008; Weijenberg et al. 2008; Gram et al. 2009; Hannan et al. 2009; Leufkens et al. 2011; Gong et al. 2012; Nishihara et al. 2013; Ordonez-Mena et al. 2016). In most of these studies (Chao et al. 2000; Rohan et al. 2000; Limburg et al. 2003; Kenfield et al. 2008; Weijenberg et al. 2008; Hannan et al. 2009; Leufkens et al. 2011; Gong et al. 2012; Ordonez-Mena et al. 2016), the RR point estimates for the categories with the greatest number of years since smoking cessation (ranging from ≥10 years to ≥40 years) were lower than those for categories with fewer number of years since cessation.

The influence of smoking cessation on the risk of colorectal cancer may be most clearly observable in analyses that focus on smoking-related molecular subtypes, including colorectal tumors with microsatellite instability (MSI-high) and the cytosine-phosphate-guanine (CpG) island methylator phenotype (CIMP-high). Several studies have associated smoking with about a two-fold increase in risk of MSI-high and CIMP-high colorectal cancer, but not with risk of other subtypes of colorectal cancer (Campbell et al. 2017). To date, only Nishihara and colleagues (2013) have examined time since smoking cessation by molecular subtype. In their study, smoking cessation, compared with continued smoking, was associated with considerably lower risk of MSI-high and CIMP-high colorectal cancer starting 10–20 years after cessation, but risk of other subtypes of colorectal cancer was similar in current and former smokers and did not change with number of years since smoking cessation.

Liver

The 2014 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between cigarette smoking and liver cancer (USDHHS 2014). Potential biological mechanisms include long-term direct exposure of the liver to carcinogens in tobacco smoke and smoking-induced fibrosis and cirrhosis (USDHHS 2014).

A meta-analysis of 23 studies was carried out for the 2014 Surgeon General's report. The meta-analysis provided estimates of the RR for liver cancer for current and former cigarette smokers compared with never

Table 4.5 Cohort studies of colorectal cancer incidence or mortality, by number of years since smoking cessation

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Chao et al. (2000)	• Cohort study (Cancer Prevention Study II) • 781,351 men and women ≥30 years of age • 4,432 deaths from colorectal cancer • United States • Follow-up period: 1982–1996	• Current smoker: – Men: 1.32 (1.16–1.49) – Women: 1.41 (1.26–1.58) • Number of years since smoking cessation (men and women): – Never smoker: 1.00 (referent) – ≤10: 1.32 (1.19–1.47) – 11–19: 1.20 (1.08–1.35) – ≥20: 1.04 (0.94–1.16) – p trend among former smokers: 0.0001	Adjusted for age; race; level of education; family history of colorectal cancer; exercise; aspirin and multivitamin use; alcohol use; and intake of vegetables, high-fiber grain foods, and fatty meats Models among women also included hormone replacement therapy Presented only sex-specific RRs for current smokers compared with never smokers
Rohan et al. (2000)	• Cohort study (Canadian National Breast Screening Study) • 56,837 women 40–59 years of age • 90 deaths from colorectal cancer • Canada • Follow-up period: 1982–1993	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.15 (0.61–2.16) – Former smoker: 1.52 (0.91–2.56) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – 1–10: 1.74 (0.91–3.33) – ≥11: 1.33 (0.70–2.57)	Adjusted for age; BMI; hours per week of vigorous activity; and intake of dietary fiber, calcium, and alcohol; and energy level
Limburg et al. (2003)	• Cohort study (Iowa Women's Health Study) • 34,467 women 55–69 years of age • 869 cases of colorectal cancer • Iowa • Follow-up period: 1986–1999	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.10 (0.89–1.37) – Former smoker: 1.21 (1.01–1.45) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – <10: 1.21 (0.93–1.56) – 10–19: 1.08 (0.77–1.51) – 20–29: 1.51 (1.09–2.09) – – >30: 1.07 (0.71–1.62) – p trend among former smokers: 0.14	Adjusted for age; BMI; waist-to-hip ratio; physical activity; alcohol consumption; hormone replacement therapy; and intake of methionine, total calories, total fat, sucrose, red meat, calcium, folate, and vitamin E

Table 4.5 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Ozasa (2007)	• Cohort study (Japan Collaborative Cohort Study for Evaluation of Cancer) • 381 deaths from colon cancer and 226 deaths from rectal cancer • Japan • Follow-up period: starting in 1988	• Men, colon: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.18 (0.80–1.72) ○ Former smoker: 1.27 (0.85–1.91) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ <5: 2.05 (1.23–3.42) ○ 5–14: 0.96 (0.55–1.68) ○ ≥15: 1.27 (0.74–2.17) • Men, rectum: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.31 (0.85–2.01) ○ Former smoker: 0.95 (0.58–1.53) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ <5: 0.50 (0.19–1.31) ○ 5–14: 1.16 (0.64–2.10) ○ ≥15: 1.00 (0.51–1.96) • Women, colon: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 0.67 (0.29–1.53) ○ Former smoker: 2.05 (0.95–4.41) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ <5: 3.74 (1.19–11.8) ○ 5–14: 0.77 (0.10–5.56) ○ ≥15: 2.14 (0.52–8.68) • Women, rectum: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.31 (0.52–3.29) ○ Former smoker: 0.68 (0.09–4.95) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ <5: 2.93 (0.40–21.3) ○ 5–14: Not reported ○ ≥15: Not reported	Adjusted for age and area of study

Table 4.5 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Kenfield et al. (2008)	• Cohort study (Nurses' Health Study) • 104,519 women 30–55 years of age • 578 deaths from colorectal cancer • United States (11 states) • Follow-up period: 1980–2004	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.63 (1.29–2.05) – Former smoker: 1.23 (1.02–1.49) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – Current smoker: 0.76 (0.55–1.05) – <10: 0.95 (0.70–1.29) – 10–19: 0.70 (0.53–0.93) – ≥20: 0.62 (0.49–0.77) – p trend among former smokers: 0.40	Adjusted for age; follow-up period; history of hypertension, diabetes, and high cholesterol; BMI; change in weight from 18 years of age to baseline; alcohol intake; physical activity; use of oral contraception; hormone replacement therapy and menopausal status; parental history of myocardial infarction before 60 years of age; number of cigarettes smoked per day; age started smoking; servings of beef, pork, lamb, or processed meat; total calcium and folate intake; and duration of aspirin use All covariates updated until diagnosis
Weijenberg et al. (2008)	• Case-cohort study (subset of the Netherlands • Cohort Study) • Men and women 55–69 years of age • 4,083 persons in subcohort and 648 cases • of colorectal cancer • The Netherlands • Follow-up period: 1989–1994	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 0.81 (0.62–1.05) – Former smoker: 1.22 (0.97–1.53) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – <10: 0.96 (0.76–1.22) – 10–30: 1.24 (0.96–1.61) – >30: 0.78 (0.45–1.33) – p = 0.33	Adjusted for age, sex, family history of colorectal cancer, BMI, and alcohol and coffee consumption
Gram et al. (2009)	• Cohort study (The Norwegian Women and Cancer study) • 68,160 women 30–69 years of age • 425 cases of colorectal cancer • Norway • Follow-up period: 1996–2005	• Smoking status: – Never smoker: 1.0 (referent) – Current smoker: 1.2 (0.9–1.5) – Former smoker: 1.3 (1.0–1.6) • Number of years since smoking cessation: – Never smoker: 1.0 (referent) – Current smoker: 1.2 (1.0–1.5) – 1–9: 1.1 (0.8–1.7) – 10–19: 1.5 (1.1–2.1) – ≥20: 1.1 (0.8–1.5)	Adjusted for age, menopausal status, use of hormonal contraceptives and postmenopausal hormonal therapy, BMI, and alcohol consumption

Table 4.5 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Hannan et al. (2009)	Cohort study (CPS-II Nutrition Cohort) • 124,751 men and women, most 50–74 years of age • 1,962 cases of colorectal cancer • United States (21 states) • Follow-up period: 1992–2005	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.27 (1.06–1.52) – Former smoker: 1.23 (1.11–1.36) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – 1–10: 1.48 (1.27–1.73) – 11–20: 1.33 (1.14–1.55) – 21–30: 1.28 (1.10–1.49) – ≥31: 1.03 (0.89–1.19) – p trend among former smokers: 0.0003	Adjusted for age, BMI, level of education, family history of colorectal cancer, physical activity, race, aspirin use, alcohol use, vegetable consumption, fiber and whole grain consumption, red and processed meat consumption, and history of endoscopy
Leufkens et al. (2011)	• Cohort study (European Prospective Investigation into Cancer and Nutrition) • 465,879 men and women, most 35–70 years of age • 2,741 cases of colorectal cancer • 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom) • Follow-up period: 1991–2000	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.08 (0.96–1.21) – Former smoker: 1.17 (1.07–1.29) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – ≤4: 1.15 (0.95–1.40) – 5–9: 1.16 (0.95–1.40) – 10–14: 1.24 (1.03–1.49) – 15–19: 1.34 (1.12–1.60) – 20–24: 1.11 (0.91–1.35) – ≥25: 1.08 (0.92–1.26) – p trend among former smokers: 0.52	Adjusted for center, age, sex, weight, height, physical activity, level of education, intake of energy from fat and nonfat, fiber, fruit, vegetables, red meat, processed meat, alcohol, and fish
Gong et al. (2012)	• Pooled analysis of eight studies from the Genetics and Epidemiology of Colorectal Cancer Consortium (Health Professionals Follow-up Study; Nurses' Health Study; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; VITamins and Lifestyle Study; Women's Health Initiative; Colon Cancer Family Registry; Diet, Activity, and Lifestyle Survey; and Ontario Familial Colorectal Cancer Registry) • Men and women • 6,796 cases of colorectal cancer and 7,770 controls	• Number of years since smoking cessation: – Never smoker: 1.00 (referent) – Current smoker: 1.36 (1.12–1.64) – <15: 1.47 (1.21–1.78) – 15–24: 1.31 (1.07–1.60) – 25–34: 1.15 (0.85–1.55) – ≥35: 0.74 (0.47–1.18)	Adjusted for age, sex, BMI, level of education, alcohol intake, and study site Number of years since smoking cessation additionally adjusted for pack-years of smoking

Table 4.5 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Nishihara et al. (2013)	• Two cohort studies: – Men from the Health Professionals Follow-up Study – Women from the Nurses' Health Study • 134,204 men and women • 1,260 cases of colorectal cancer with available tumors • United States • Follow-up period: – Nurses' Health Study: 1980–2008 – Health Professionals Follow-up Study: 1986–2008	• Colorectal cancer (all): – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.17 (0.96–1.43) ○ Former smoker: 1.18 (1.05–1.34) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ 1–4: 0.99 (0.73–1.34) ○ 5–9: 1.30 (0.99–1.71) ○ 10–19: 0.96 (0.75–1.23) ○ 20–39: 0.92 (0.74–1.14) ○ ≥40: 1.05 (0.80–1.37) • CIMP-high: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 2.08 (1.35–3.20) ○ Former smoker: 1.30 (0.95–1.76) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ 1–4: 1.09 (0.58–2.02) ○ 5–9: 0.89 (0.48–1.66) ○ 10–19: 0.52 (0.29–0.93) ○ 20–39: 0.52 (0.32–0.84) ○ ≥40: 0.48 (0.26–0.90)	Adjusted for calendar year, age, sex, BMI, family history of colorectal cancer, regular use of aspirin, physical activity level, alcohol consumption, total caloric intake, and intake of red meat Focused on molecular subtypes of colorectal cancer previously established to be smoking related, including CIMP-high

Table 4.5 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)[b]	Comments
Ordonez-Mena et al. (2016)	• Collaboration of 19 prospective cohort studies • 897,021 men and women • 12,696 cases of colorectal cancer and 4,878 deaths from colorectal cancer • Europe and United States	• Incidence of colorectal cancer: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.20 (1.07–1.34) ○ Former smoker: 1.20 (1.15–1.25) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ ≤9: 1.00 (0.87–1.16) ○ 10–19: 1.11 (0.97–1.27) ○ ≥20: 0.88 (0.78–1.00) • Mortality from colorectal cancer: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.35 (1.16–1.58) ○ Former smoker: 1.22 (1.13–1.31) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ ≤9: 1.07 (0.86–1.32) ○ 10–19: 1.07 (0.87–1.31) • ≥20: 0.76 (0.63–0.93)	Analyses of number of years since smoking cessation included only cohorts with these data and therefore included substantially fewer participants Adjusted for sex, age, BMI, level of education, vigorous physical activity, history of diabetes, and alcohol consumption

Notes: **BMI =** body mass index; **CI =** confidence interval; **CIMP-high =** cytosine-phosphate-guanine island methylator phenotype; **CPS =** Cancer Prevention Study; **RR =** relative risk.

[a]Studies are of cancer incidence unless number of cancer deaths is identified.

[b]p trend values are shown only if described as being among former smokers.

smokers. This meta-analysis reported a lower summary RR for former smokers (1.4; 95% CI, 1.1–1.7) than for current smokers (1.7; 95% CI, 1.5–1.9). Seven other studies published in 2014 or later found similar results (Everatt et al. 2014; Moura et al. 2014; Chen et al. 2015; Meyer et al. 2015; Pang et al. 2015; Chiang et al. 2016; Niu et al. 2016). Of the 30 studies overall, only 4 (all case-control studies) reported information on risk by number of years since smoking cessation (Table 4.6) (Choi and Kahyo 1991; Goodman et al. 1995; Ozasa 2007; Hassan et al. 2008). Results from these studies are inconsistent and are limited by small samples, as the largest (Hassan et al. 2008) included only 154 cases of liver cancer among former smokers.

Cervix

The 1990 Surgeon General's report concluded that "risk of cervical cancer is substantially lower among former smokers in comparison with continuing smokers, even in the first few years after cessation" (USDHHS 1990, p. 10). However, it did not explicitly conclude that smoking cessation reduced risk of cervical cancer. The 2004 Surgeon General's report concluded that there was sufficient evidence to infer a causal relationship between cigarette smoking and cervical cancer (USDHHS 2004). The association between smoking and higher risk of cervical cancer persists when adjusted for measures of infection with the human papillomavirus (HPV) (IARC 2012; Roura et al. 2014). Potential biological mechanisms include direct genotoxic effects of nitrosamines and polyaromatic hydrocarbons from tobacco smoke and suppression of the immune system, including reduced ability to clear infection caused by HPV (Fonseca-Moutinho 2011; Gadducci et al. 2011).

In a meta-analysis of more than 20 studies published through 2003 that used never smokers as the reference group, Gandini and colleagues (2008) found that RRs for cervical cancer were lower for former smokers (1.26; 95% CI, 1.11–1.42) than for current smokers (1.83; 95% CI, 1.51–2.21) (Roura et al. 2014). Earlier, the International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC) (2006) conducted a large pooled analysis of 23 studies (8 cohort, 15 case control) that included data from most of the studies published up to that time. In that analysis, summary RRs for squamous cell carcinoma, by far the most common histologic type of cervical cancer (American Cancer Society 2016), were lower for former smokers (1.12; 95% CI, 1.01–1.25) than for current smokers (1.60; 95% CI, 1.48–1.73). Smoking was not associated with adenocarcinoma of the cervix (0.89; 95% CI, 0.74–1.06), which accounts for a small proportion of cervical cancers (American Cancer Society 2016). RRs have also been greater for current smokers than for former smokers in studies published after 2006 (Odongua et al. 2007; Madsen et al. 2008; Roura et al. 2014).

Using data from a subset of studies in its pooled analysis, ICESCC (2006) reported on the risk of cervical cancer by number of years since smoking cessation. Table 4.7 summarizes these results and results from two other studies published since 2004, including a case-control study (Shields et al. 2004) and a cohort study (Roura et al. 2014). In the pooled analysis, estimates of RR were slightly lower for having quit 10 or more years ago versus having done so more recently, although trends by number of years since smoking cessation were not statistically significant. The cohort study (Roura et al. 2014), which was conducted in Europe among 308,036 women, included 261 cases of invasive cervical cancer and 804 cases of carcinoma in situ (CIS) or cervical intraepithelial cancer grade 3 (CIN3). For both invasive cancer and CIS/CIN3, Roura and colleagues (2014) found statistically significant decreases in risk as the number of years since quitting increased, with risk reaching less than or about half that in current smokers among women who had quit smoking 20 or more years earlier. Finally, Shields and colleagues (2004), in a case-control study conducted in five U.S. cities, did not find any trends related to number of years since quitting; however, their study included relatively few former smokers.

Kidney

The 2004 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between cigarette smoking and kidney cancer (USDHHS 2004). Biological mechanisms for such a relationship may include oxidative stress (Patel et al. 2015) and exposure to nitrosamines and other carcinogens in tobacco smoke (USDHHS 2004; Clague et al. 2009).

In a meta-analysis of more than 20 studies of smoking and incident kidney cancer, Cumberbatch and colleagues (2016) found that the RR for kidney cancer, in comparisons with never smokers, was lower for former smokers (RR = 1.16; 95% CI, 1.08–1.25) than for current smokers (RR = 1.36; 95% CI, 1.19–1.56). Finally, 10 studies, all case-control, examined risk for kidney cancer by time since quitting among former smokers (Table 4.8) (McLaughlin et al. 1984, 1995; La Vecchia et al. 1990; McCredie and Stewart 1992; Kreiger et al. 1993; Muscat et al. 1995; Yuan et al. 1998; Parker et al. 2003; Hu et al. 2005; Cote et al. 2012). In most of these studies, the odds ratio (OR) for the highest category of number of years since quitting (ranging from >10 to >30 years) was lower than the OR for categories with fewer years since quitting.

Acute Myeloid Leukemia

The 2004 Surgeon General's report concluded that the evidence was sufficient to infer a causal relationship between smoking and AML (USDHHS 2004). Potential

Table 4.6 Studies of liver cancer incidence or mortality, by number of years since smoking cessation

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
Choi et al. (1991)	• Case-control, hospital-based study • 216 cases of liver cancer in males and 648 male controls • Korea • Time period in which cases were diagnosed: 1986–1990	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.01 (0.65–1.57) – Former smoker: 0.65 (0.35–1.19) • Number of years since smoking cessation: – Current smoker: 1.00 (referent) – 1–4: 0.76 (0.31–1.89) – 5–9: 0.43 (0.15–1.26) – ≥10: 0.44 (0.11–1.82)	Adjusted for age, marital status, level of education, serum hepatitis B virus surface antigen, and alcohol consumption
Goodman et al. (1995)	• Cohort study (Life Span Study) • 36,133 men and women who were in Hiroshima or Nagasaki at the time of the atomic bombings in August 1945 • 242 cases of liver cancer • Japan • Follow-up period: 1980–1989	• Men: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 4.26 (1.87–9.72) ○ Former smoker: 4.56 (1.95–10.7) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ <14: 5.60 (2.15–14.6) ○ 14–23: 4.11 (1.58–10.7) ○ ≥24: 4.04 (1.54–10.6) • Women: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.58 (0.86–2.88) ○ Former smoker: 1.66 (0.76–3.63) – Number of years since smoking cessation: ○ Never smoker: 1.00 (referent) ○ <10: 10.4 (2.51–43.5) ○ 10–24: 1.03 (0.25–4.24) ○ ≥25: 2.31 (0.72–7.43)	Adjusted for city, age at time of the atomic bombings, attained age, and radiation dose to the liver

Table 4.6 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
Ozasa (2007)	• Cohort study (Japan Collaborative Cohort Study for Evaluation of Cancer) • 620 deaths from liver cancer • Japan • Follow-up period: starting in 1988	• Men: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.59 (1.20–2.12) ○ Former smoker: 1.48 (1.09–2.00) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ <5: 1.27 (0.81–1.98) ○ 5–14: 1.54 (1.06–2.23) ○ ≥15: 1.54 (1.05–2.27) • Women: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.95 (1.19–3.19) ○ Former smoker: 0.76 (0.24–2.39) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ <5: 1.05 (0.14–7.51) ○ 5–14: 1.40 (0.34–5.69) ○ ≥15: Not reported	Adjusted for age and area of study
Hassan et al. (2008)	• Case-control, hospital-based study • 319 cases of liver cancer among men and women treated at MD Anderson Cancer Center, and 1,061 controls who were relatives of the patients • Houston, Texas • Time period in which cases were diagnosed: 2000–2006	• Number of years since smoking cessation: – Never smoker: 1.0 (referent) – ≤10: 1.7 (1.0–3.1) – >10: 1.3 (0.8–1.9)	Adjusted for age, race, level of education, marital status, state of residency, hepatitis B virus, hepatitis C virus, diabetes, heavy alcohol consumption, and family history of cancer Did not present results by smoking status

Notes: **CI =** confidence interval; **RR =** relative risk.

[a]Studies are of cancer incidence unless the number of cancer deaths is identified.

Table 4.7 Studies of cervical cancer incidence by years since smoking cessation

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
International Collaboration of Epidemiological Studies of Cervical Cancer (2006)	• Collaborative analysis of 23 cohort and case-control studies (The International Collaboration of Epidemiological Studies of Cervical Cancer) • 9,052 cases of invasive cancer (7,498 with data on number of years since smoking cessation), 4,489 cases of carcinoma in situ or cervical intraepithelial neoplasia III, and 23,017 controls • Studies from Algeria, Brazil, Chile, Colombia, Costa Rica, Denmark, India, Italy, Mali, Mexico, Morocco, Norway, Panama, Paraguay, Peru, Philippines, South Africa, Spain, Sweden, Thailand, United Kingdom, and United States	• Number of years since smoking cessation: – Invasive cancer: ○ Never smoker: 1.00 (0.94–1.06) ○ Current smoker: 1.46 (1.35–1.58) ○ 1–4: 1.05 (0.87–1.28) ○ 5–9: 1.08 (0.85–1.38) ○ ≥10: 0.99 (0.83–1.18) – Carcinoma in situ or cervical intraepithelial neoplasia III: ○ Never smoker: 1.00 (0.91–1.10) ○ Current smoker: 1.83 (1.68–1.99) ○ 1–4: 1.35 (1.05–1.74) ○ 5–9: 1.35 (0.99–1.83) ○ ≥10: 1.19 (0.85–1.66)	Cohort studies analyzed as nested case-control studies, with up to four controls selected randomly per case according to age Adjusted for study, study center, age, age at first intercourse, duration and use of oral contraception, number of full-term pregnancies, and lifetime number of sexual partners
Shields et al. (2004)	• Case-control, population-based study • Women 20–74 years of age • 235 cases of squamous cell carcinoma and 209 controls with seropositive human papillomavirus • Controls obtained from random-digit dialing • Time period in which cases were diagnosed: 1982–1984 • Five U.S. cities (Birmingham, Chicago, Denver, Miami, and Philadelphia)	• Smoking status: – Never smoker: 1.0 (referent) – Current smoker: 1.9 (1.2–2.8) – Former smoker: 1.4 (0.8–2.4) • Number of years since smoking cessation: – 1–5: 1.0 (referent) – 6–14: 0.6 (0.2–2.0) – ≥15: 0.8 (0.3–2.5)	Cases restricted to squamous cell carcinoma

Table 4.7 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
Roura et al. (2014)	• Cohort study (European Prospective Investigation into Cancer and Nutrition) • 308,036 women, most 35–70 years of age • 261 cases of ICC and 804 cases of CIS or CIN3 • 10 European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and United Kingdom) • Follow-up period: 1992–2006	• Smoking status: – ICC: ○ Never smoker: 1.0 (referent) ○ Current smoker: 1.9 (1.4–2.5) ○ Former smoker: 1.5 (1.1–2.1) – CIS or CIN3: ○ Never smoker: 1.0 (referent) ○ Current smoker: 2.1 (1.8–2.5) ○ Former smoker: 1.5 (1.2–1.8) – p trend among former smokers: 0.02 • Number of years since smoking cessation: – ICC: ○ Current smoker: 1.0 (referent) ○ ≤4: 1.2 (0.7–2.0) ○ 5–9: 0.9 (0.5–1.7) ○ 10–19: 0.8 (0.5–1.3) ○ ≥20: 0.4 (0.2–0.8) – CIS or CIN3: ○ Current smoker: 1.0 (referent) ○ ≤4: 0.8 (0.6–1.1) ○ 5–9: 1.0 (0.7–1.3) ○ 10–19: 0.5 (0.4–0.8) ○ ≥20: 0.5 (0.3–0.7) • Statistically significant p trends for the association between smoking-related variables and the risk of CIN3/CIS and ICC by risk factor: – Smoking duration (years); p trends among ever smokers: <0.0001 (CIN3/CIS), 0.08 (ICC) – Lifetime smoking intensity (cig/day); – p trend among ever smokers: 0.07 (ICC) – Smoking pack years; p trends among ever smokers: 0.001 (CIN3/CIS); 0.07 (ICC) – Time since quitting; p trends among past smokers: 0.02 (CIN3/CIS); 0.02 (ICC)	Adjusted for BMI, marital status, level of education, physical activity, number of full-term pregnancies, and use and duration of oral contraception

Notes: **BMI =** body mass index; **CI =** confidence interval; **CIN3 =** cervical intraepithelial neoplasia III;
[a]Studies are of cancer incidence unless the number of cancer deaths is identified.

Table 4.8 Studies of kidney cancer incidence by number of years since smoking cessation

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
McLaughlin et al. (1984)	• Case-control, population-based study • White men and women 30–85 years of age • 495 cases of kidney cancer and 697 controls • Time period in which cases were diagnosed: 1974–1979 • Minneapolis-St. Paul, Minnesota, metropolitan area	• Number of years since smoking cessation: – Men: ○ Never smoker: 1.0 (referent): ○ ≤10 prior to 1974: 1.7 ○ >10 prior to 1974: 1.1 ○ Current smoker: 1.8 – Women: ○ Never smoker: 1.0 (referent) ○ ≤10 prior to 1974: 1.7 ○ >10 prior to 1974: 1.6 ○ Current smoker: 2.0	Adjusted for age Confidence intervals not provided
LaVecchia et al. (1990)	• Case-control, hospital-based study • Cases: Men and women <75 years of age • Controls: Admitted for acute conditions • 131 cases of kidney cancer and 394 controls • Time period in which cases were diagnosed: 1985–1989 • Northern Italy	• Number of years since smoking cessation: – Never smoker: 1.0 (referent) – <10: 2.2 (1.1–4.4) – ≥10: 1.3 (0.6–2.7)	Adjusted for age, sex, area of residence, level of education, and BMI Did not present results for current smoking status
McCredie et al. (1992)	• Case-control, population-based study • Men and women 20–79 years of age • 489 cases of kidney cancer and 523 controls • Time period in which cases were diagnosed: 1989–1990 • New South Wales, Australia	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 2.17 (1.55–3.02) – Former smoker: 1.41 (1.03–1.95) • Number of years since smoking cessation: – Current smoker: 1.00 (referent) – 1–12: 0.85 (0.53–1.38) – 13–24: 0.89 (0.52–1.53) – ≥25: 0.47 (0.22–1.00)	Adjusted for age, sex, method of interview, and BMI Number of years since smoking cessation additionally adjusted for duration of cigarette smoking and number of cigarettes smoked per day

Table 4.8 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
Kreiger et al. (1993)	• Case-control, population-based study • Men and women 25–69 years of age • 518 cases of kidney cancer and 1,381 controls • Time period in which cases were diagnosed: • 1994–1997 • Ontario, Canada	• Number of years since smoking cessation: – Men: ○ Never smoker: 1.0 (referent) ○ Current smoker: 2.3 (1.5–3.4) ○ 1–4: 2.1 (1.2–3.8) ○ 5–9: 1.8 (1.0–3.3) ○ 10–19: 2.1 (1.3–3.4) ○ ≥20: 1.3 (0.8–2.1) – Women: ○ Never smoker: 1.0 (referent) ○ Current smoker: 2.2 (1.5–3.2) ○ 1–4: 1.4 (0.6–2.9) ○ 5–9: 1.6 (0.7–3.7) ○ 10–19: 1.9 (0.8–4.2) ○ ≥20: 1.5 (0.7–3.1)	Adjusted for age and BMI
McLaughlin et al. (1995)	• Case-control, population-based study • Men and women 20–79 years of age • 1,732 cases of kidney cancer and 2,309 controls • Time period in which cases were diagnosed: 1989–1991 • Six study centers in five countries: Australia (Sydney), Denmark, Germany (Berlin and Heidelberg), Sweden (Uppsala), and United States (Minnesota)	• Smoking status: – Never smoker: 1.0 (referent) – Current smoker: 1.4 (1.2–1.7) – Former smoker: 1.2 (1.0–1.4) • Number of years since smoking cessation: – Current smoker: 1.0 (referent) – ≤5: 0.90 (0.7–1.2) – 6–15: 0.84 (0.7–1.1) – 16–25: 0.75 (0.6–1.0) – >25: 0.85 (0.6–1.1)	Adjusted for age, sex, study center, and BMI Number of years since smoking cessation additionally adjusted for number of cigarettes smoked per day

Table 4.8 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
Muscat et al. (1995)	• Case-control, hospital-based study • Cases: Men and women diagnosed at hospitals in the study areas • Controls: Hospitalized for conditions unrelated to tobacco use • 788 cases of kidney cancer and 779 controls • Time period in which cases were diagnosed: 1977–1993 • Multicenter hospitals in New York (New York City and New Hyde Park), Illinois (Chicago and Hines), Michigan (Detroit), and Pennsylvania (Philadelphia)	• Men: – Smoking status: ○ Never smoker: 1.0 (referent) ○ Current smoker: 1.4 (1.02–2.0) ○ Former smoker: 0.9 (0.7–1.5) – Number of years since smoking cessation: ○ Never smoker: 1.0 (referent) ○ 1–5: 1.6 (0.9–2.6) ○ 6–10: 2.2 (1.2–4.4) ○ >10: 0.7 (0.5–0.9) • Women – Smoking status: ○ Never smoker: 1.0 (referent) ○ Current smoker: 1.0 (0.7–1.6) ○ Former smoker: 1.1 (0.7–1.7) – Number of years since smoking cessation: ○ Never smoker: 1.0 (referent) ○ 1–5: 1.0 (0.4–2.2) ○ 6–10: 1.3 (0.3–6.0) ○ >10: 1.1 (0.6–1.8)	Adjusted for age and level of education
Yuan et al. (1998)	• Case-control, population-based study • Non-Asian men and women 25–74 years of age • 1,204 cases of kidney cancer and 1,204 controls • Time period in which cases were diagnosed: 1986–1994 • Los Angeles, California	• Smoking status: – Never smoker: 1.00 (referent) – Current smoker: 1.53 (1.23–1.90) – Former smoker: 1.24 (1.02–1.50) • Number of years since smoking cessation: – Never smoker: 1.00 (referent) – 1–9: 1.33 (1.02–1.74) – 10–19: 1.25 (0.94–1.64) – ≥20: 1.15 (0.89–1.50)	Adjusted for level of education
Parker et al. (2003)	• Case-control, population-based study • Men and women 40–85 years of age • 387 cases of kidney cancer and 2,333 controls • Time period in which cases were diagnosed: 1985–1987 • Iowa	• Number of years of smoking cessation: – Current smoker: 1.00 (referent) – Never smoker: 0.6 (0.4–0.9) – <10: 0.7 (0.4–1.1) – 10–19: 0.8 (0.5–1.2) – 20–29: 0.7 (0.4–1.1) – ≥30: 0.5 (0.3–1.0)	Adjusted for age, sex, BMI, history of hypertension, and pack-years of smoking

Table 4.8 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
Hu et al. (2005)	• Case-control, population-based study • Men and women 20 years of age and older • 1,279 cases of kidney cancer and 5,370 controls • Time period in which cases were diagnosed: 1994–1997 • Eight Canadian provinces: Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan	• Men: – Smoking status: ○ Never smoker: 1.0 (referent) ○ Current smoker: 0.9 (0.7–1.2) ○ Former smoker: 1.2 (1.0–1.5) – Number of years since smoking cessation: ○ Never smoker: 1.0 (referent) ○ ≤10: 1.5 (1.0–2.3) ○ 11–20: 1.1 (0.8–1.5) ○ 21–30: 1.2 (0.8–1.6) ○ ≥31: 1.0 (0.7–1.4) • Women: – Smoking status: ○ Never smoker: 1.0 (referent) ○ Current smoker: 0.9 (0.7–1.2) ○ Former smoker: 1.3 (1.0–1.6) – Number of years since smoking cessation: ○ Never smoker: 1.0 (referent) ○ ≤10: 1.5 (0.8–2.6) ○ 11–20: 0.6 (0.4–1.1) ○ ≥20: 1.1 (0.7–1.6)	Adjusted for age; Canadian province; level of education; BMI; alcohol use; and consumption of meats, vegetables, and fruits Number of years since smoking cessation additionally adjusted for pack-years of smoking

Table 4.8 Continued

Study	Design/population[a]	Exposure estimates: RR (95% CI)	Comments
Cote et al. (2012)	• Case-control, population-based study • Men and women 20–79 years of age • 1,217 cases of kidney cancer and 1,235 controls • Time period in which cases were diagnosed: 2002–2007 • Detroit (Michigan) and Chicago (Illinois)	• White: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.46 (1.05–2.04) ○ Former smoker: 0.99 (0.78–1.25) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ ≤5: 1.34 (0.83–2.17) ○ 6–15: 0.82 (0.53–1.25) ○ 16–25: 0.61 (0.39–0.94) ○ ≥25: 0.62 (0.39–1.01) • Black: – Smoking status: ○ Never smoker: 1.00 (referent) ○ Current smoker: 1.16 (0.81–1.65) ○ Former smoker: 0.81 (0.56–1.18) – Number of years since smoking cessation: ○ Current smoker: 1.00 (referent) ○ ≤5: 0.97 (0.51–1.85) ○ 6–15: 0.73 (0.42–1.26) ○ 16–25: 0.72 (0.38–1.37) ○ ≥25: 0.47 (0.25–0.88)	Adjusted for age, study site, sex, BMI, education level, family history of kidney cancer, and hypertension Number of years since smoking cessation additionally adjusted for pack-years of smoking

Notes: **BMI =** body mass index; **CI =** confidence interval; **OR =** odds ratio.
[a]Studies are of cancer incidence unless number of cancer deaths is identified.

mechanisms include inhalation of benzene, a known cause of leukemia, and radioactive substances in tobacco smoke (Thomas and Chelghoum 2004; USDHHS 2004; Lichtman 2007).

In a meta-analysis of 5 cohort and 12 case-control studies of smoking and AML, Colamesta and colleagues (2016) reported separate summary RRs for cohort and case-control studies. For the cohort studies, summary RR estimates were 1.45 (95% CI, 1.08–1.94) for former smokers and 1.52 (95% CI, 1.10–2.14) for current smokers. For the case-control studies, summary RRs were 1.21 (95% CI, 1.03–1.41) for former smokers and 1.36 (95% CI, 1.11–1.66) for current smokers. This meta-analysis also pooled data that included information on number of years since cessation from three case-control studies (Severson et al. 1990; Kane et al. 1999; Musselman et al. 2013). In the pooled analysis, risk declined with increasing time since smoking cessation, with no statistically significant reduction in risk among former smokers who had quit within 10 years compared with continuing smokers (OR = 1.01; 95% CI, 0.60–1.72). The risk was lower for those who had quit for 10–20 years (OR = 0.74; 95% CI, 0.53–1.03) and even lower for those who had quit for more than 20 years (OR = 0.59; 95% CI, 0.45–0.78).

Synthesis of the Evidence

The 1990 Surgeon General's report concluded that smoking cessation reduces the risk of six cancers: lung, larynx, oral cavity and pharynx, esophagus, pancreas, and bladder (USDHHS 1990). Results of studies published since 1990 expand the role of smoking as a cause of cancer and support the reduction of cancer risk following smoking cessation.

The 2004 and 2014 Surgeon General's reports concluded that smoking causes at least six additional cancers beyond those for which the associations were considered causal in 1990: stomach, liver, colon and rectum, kidney, cervix, and AML (USDHHS 2004, 2014). The 12 types of cancer reviewed in this section have all been judged to be caused by cigarette smoking in reports of the U.S. Surgeon General (USDHHS 2014) and IARC (IARC 2012)—based on evaluating the evidence against criteria for causality utilized in Surgeon Generals' reports, including consistency across studies, temporal relationship of association, strength of association, and biological plausibility (USDHHS 2004).

These same criteria have been used to evaluate the evidence on smoking cessation. Because smoking cessation reduces cumulative exposure to tobacco smoke across the life course, biological plausibility alone, coupled with appropriate temporality, supports the conclusion that smoking cessation reduces the risk of all 12 cancers that have been causally linked to cigarette smoking. Additionally, epidemiological evidence documents that the risk for most of these cancers drops progressively as the time since successful quitting lengthens, and findings are generally consistent across studies.

The effect of smoking cessation on risk for lung cancer is particularly important because lung cancer is the largest contributor to smoking-attributable cancer mortality in the United States and the number of new cases continues to increase (U.S. Cancer Statistics Working Group 2019). Since 1990, many studies have been published characterizing how risk for lung cancer changes with time since smoking cessation. As noted previously, results from many studies (Calle et al. 2002; IARC 2007; Pinsky et al. 2015) indicate that, in comparison with smokers who do not quit, RRs for lung cancer decline steadily after smoking cessation, with RRs for former smokers falling to half those of RRs for continuing smokers after approximately 10–15 years of cessation.

While the 2004 and 2014 Surgeon General's reports concluded that smoking causes cancers of the stomach, colon and rectum, kidney, and cervix and AML (USDHHS 2004, 2014), the two reports did not explicitly conclude that smoking cessation reduces the risk for these cancers. For four of these malignancies (stomach, kidney, cervix, and AML), RRs are consistently lower among former cigarette smokers than among current smokers, supporting a causal association between smoking cessation and lower risk for these cancers. Similarly, the 2004 and 2014 Surgeon General's reports also concluded that smoking causes cancer of the liver (USDHHS 2004, 2014). This report considered four specific studies showing that RRs decline in former smokers with time since smoking cessation. These findings were consistent with the meta-analysis of 29 studies conducted for the 2014 Surgeon General's report that documented a much lower RR in former smokers than in current smokers, compared with never smokers (USDHHS 2014). Taken together, these epidemiological findings support a causal association between smoking cessation and lower risk for liver cancer.

In studies of colorectal cancer, RRs for former smokers have not been consistently lower than those for current smokers. However, in many of the studies where lower RRs have not been observed for former smokers, current smokers likely did not have sufficiently long induction periods to fully reflect the long-term effects of smoking. In addition to the studies where lower RRs were observed, other evidence supports the hypothesis that smoking cessation reduces risk of colorectal cancer. This evidence includes studies that document substantially lower RRs for colorectal adenoma, an established precursor lesion for colorectal cancer, among former smokers than among current smokers. These studies have also found declining RRs

for colorectal cancer among former smokers with increased time since smoking cessation, particularly for specific molecular subtypes that are associated with smoking. Taken together, these epidemiological findings, including those of incident colorectal cancer and established precursor lesions for colorectal cancer, support a causal association between smoking cessation and lower risk for colorectal cancer.

Conclusions

1. The evidence is sufficient to infer that smoking cessation reduces the risk of lung cancer.
2. The evidence is sufficient to infer that smoking cessation reduces the risk of laryngeal cancer.
3. The evidence is sufficient to infer that smoking cessation reduces the risk of cancers of the oral cavity and pharynx
4. The evidence is sufficient to infer that smoking cessation reduces the risk of esophageal cancer.
5. The evidence is sufficient to infer that smoking cessation reduces the risk of pancreatic cancer.
6. The evidence is sufficient to infer that smoking cessation reduces the risk of bladder cancer.
7. The evidence is sufficient to infer that smoking cessation reduces the risk of stomach cancer.
8. The evidence is sufficient to infer that smoking cessation reduces the risk of colorectal cancer.
9. The evidence is sufficient to infer that smoking cessation reduces the risk of liver cancer.
10. The evidence is sufficient to infer that smoking cessation reduces the risk of cervical cancer.
11. The evidence is sufficient to infer that smoking cessation reduces the risk of kidney cancer.
12. The evidence is sufficient to infer that smoking cessation reduces the risk of acute myeloid leukemia.
13. The evidence is sufficient to infer that the relative risk of lung cancer decreases steadily after smoking cessation compared with the risk for persons continuing to smoke, with risk decreasing to half that of continuing smokers approximately 10–15 years after smoking cessation and decreasing further with continued cessation.

Implications

The evidence that smoking cessation reduces cancer risk has long been an important part of the rationale for efforts—including educational, clinical, health systems, community, and population-based interventions and initiatives to make evidence-based, barrier-free cessation services widely available—to motivate and help smokers to quit. This report's conclusion that smoking cessation reduces the risk of several additional types of cancer further strengthens that rationale and provides an opportunity for broadening and intensifying messages about the important role that smoking cessation plays in cancer prevention.

Smoking Cessation After a Cancer Diagnosis

This section reviews evidence of the health benefits of smoking cessation at the time of a cancer diagnosis or after that diagnosis compared with continuing to smoke. At the time of cancer diagnosis, approximately 20–30% of all cancer patients self-reported current cigarette smoking (Warren and Simmons 2018); however, self-reported rates of smoking were typically lower than biochemically confirmed smoking, as smokers with cancer may misrepresent their smoking. Among long-term cancer survivors, the smoking prevalence is approximately 9% (Warren and Simmons 2018). This review is limited to all-cause mortality, an integrative indicator, and does not explore disease progression or recurrence, cancer-specific mortality, second primary cancer, quality of life, or treatment toxicity as outcomes of interest.

Conclusions from Previous Surgeon General's Reports

Previous reports of the Surgeon General have not evaluated the health benefits of smoking cessation after a cancer diagnosis, but smoking is causally associated with diseases of every major organ system and is therefore

strongly linked with all-cause mortality (USDHHS 2014). The 2014 Surgeon General's report concluded that smoking increases all-cause mortality. The 2014 report was also the first to conclude that continued smoking after a cancer diagnosis causes adverse health outcomes among cancer patients or survivors (i.e., persons who have been diagnosed with cancer) (U.S. Department of Health and Human Services [USDHHS] 2014). Smoking cessation has been shown to reduce all-cause mortality in the general population (USDHHS 2014), providing strong justification for the hypothesis that cessation after a cancer diagnosis will result in improved survival compared with continued smoking. Given the conclusions in the 2014 Surgeon General's report about the adverse health effects that cancer patients who smoke can experience, a review of the evidence on smoking cessation after a cancer diagnosis is important.

Literature Review Methods

The literature search for this section followed the strategy used in the 2014 Surgeon General's report (USDHHS 2014), which queried the National Library of Medicine's MEDLINE database for "smoking" and "cancer." Studies were considered for inclusion if they met three criteria:

- They were original reports that compared all-cause mortality between (a) current smokers who were diagnosed with cancer but continued smoking and (b) patients who had quit smoking within 1 year of a cancer diagnosis or patients who had quit smoking after a cancer diagnosis;
- They had a baseline and final cohort size of at least 100 cancer patients, including cigarette smokers and quitters; and
- They were published from 2000 to 2016.

Studies were excluded if they reported findings on only continued smoking after a cancer diagnosis versus quitting smoking substantially before a cancer diagnosis.

Smoking Cessation and All-Cause Mortality in Cancer Patients

Ten studies (seven prospective cohort studies and three retrospective cohort studies) reporting on 10,975 patients met the inclusion criteria (Table 4.9). The studies are grouped in the table by their reference group: never smokers, current smokers who did not stop smoking with diagnosis (referred to as persistent smokers), and quitters. The cohorts were composed of patients with lung cancer (four studies), with head/neck cancer (three studies), with breast cancer (one study), and with multiple types of cancer (two studies). Eight studies did not specify the treatment modality (surgery, radiotherapy, chemotherapy), and two patient cohorts were composed exclusively of patients treated with radiotherapy (Al-Mamgani et al. 2014; Roach et al. 2016).

Three prospective cohort studies (Al-Mamgani et al. 2014; Choi et al. 2016; Passarelli et al. 2016) compared continued smoking and quitting smoking with never smoking. In all three studies, continued smoking after a cancer diagnosis significantly increased risk of mortality compared with never smoking, and the risk of mortality for quitters was greater than that for never smokers but not as great as that for continuing smokers.

Three studies (Sardari Nia et al. 2005; Sandoval et al. 2009; Chen et al. 2010) compared quitting smoking with persistent smoking using persistent smokers as the referent. Quitting was significantly associated with reduced all-cause mortality in two studies, with associations that were significant in patients with non-small cell lung cancer (relative risk [RR] = 0.34; 95% CI, 0.16–0.71) (Sardari Nia et al. 2005) and in patients with small cell lung cancer (hazard ratio [HR] = 0.55; 95% CI, 0.38–0.79) (Chen et al. 2010), but not in a study of patients with oral cavity cancer (RR = 0.92; 95% CI, 0.46–1.84) (Sandoval et al. 2009).

Four studies compared continued cigarette smoking with quitting, using quitters as the referent (Tao et al. 2013; Al-Mamgani et al. 2014; Dobson Amato et al. 2015; Roach et al. 2016). In all four studies, continued smoking was associated with increased all-cause mortality relative to quitting. For a group of 1,632 male cancer patients from the Shanghai Cancer Cohort (Tao et al. 2013), results by disease site showed (a) a significantly increased risk of all-cause mortality in persistent (continued) smokers for lung cancer (HR = 1.89; 95% CI, 1.18–3.02), colorectal cancer (HR = 3.46; 95% CI, 1.69–7.10), and bladder cancer (HR = 17.29; 95% CI, 2.25–132.64) and (b) indication of increased mortality in other cancers (HR = 1.49; 95% CI, 0.92–2.40).

Evaluation of the Evidence

This is the first review in a report of the Surgeon General on the potential health benefits of smoking cessation after a cancer diagnosis. This section considers scientific evidence with reference to five key guidelines for

Table 4.9 Cohort studies that compared all-cause mortality in persons who were smokers at the time of a cancer diagnosis but had quit smoking after the diagnosis with those who continued smoking after the diagnosis

Study	Design/population	Follow-up period	Comparison group(s)	Definitions of groups	Findings
Reference group: Never smokers					
Yang et al. (2015a)	• Prospective cohort • 2,548 patients with colorectal cancer from CPS II • 153 current smokers at baseline	• Every 2 years from 1997 to December 31, 2010	• Quitters • Persistent smokers	• **Never smokers:** Those who never smoked • **Quitters:** Those who had quit smoking after a cancer diagnosis • **Persistent smokers:** Those who continued to smoke after a cancer diagnosis	• Adjusted RR: – Never smokers: 1.0 (referent) – Quitters: 1.94 (95% CI, 1.29–2.91) – Persistent smokers: 2.33 (95% CI, 1.62–3.34) • RR for quitters vs. persistent smokers: 0.833 (p = 0.37, 1.94 vs. 2.33)
Choi et al. (2016)	• Prospective cohort • 590 patients with head or neck cancer • 146 persistent smokers at any time after a cancer diagnosis • 99 quitters • University of Michigan	• Every 3 months for 2 years • Annually after the first 2 years until 8 years of follow-up or September 11, 2011, whichever came first	• Quitters • Persistent smokers	• **Never smokers:** Those who never smoked • **Quitters:** Those who had quit within the first 3 months of diagnosis of squamous cell carcinoma (head or neck) and remained a quitter through the first 2 years after the diagnosis • **Persistent smokers:** Those who smoked at any time after a cancer diagnosis (defined as continuing smokers in the study)	• Adjusted HR: – Never smokers: 1.0 (referent) – Quitters: 2.38 (95% CI, 1.29–4.36) – Persistent smokers: 2.71 (95% CI, 1.48–4.98) • RR for quitters vs. persistent smokers: 0.877 (2.38 vs. 2.71, calculated)
Passarelli et al. (2016)	• Prospective cohort • 4,562 patients with breast cancer, as a part of the Collaborative Breast Cancer Study and Collaborative Women's Longevity Study • 424 persistent smokers • 352 quitters	• Median follow-up of 6 years after diagnosis	• Quitters • Persistent smokers	• **Never smokers**: Those who never smoked • **Quitters**: Those who had quit smoking during the year before the cancer diagnosis and remained a quitter after the diagnosis • **Persistent smokers**: Those who reported actively smoking during the year before the cancer diagnosis and after the diagnosis	• Adjusted HR: – Never smokers: 1.0 (referent) – Quitters: 2.34 (95% CI, 1.85–2.96) – Persistent smokers: 2.57 (95% CI, 2.06–3.21) • RR for quitters vs. persistent smokers: 0.911 (2.34 vs. 2.57, calculated)

Table 4.9 Continued

Study	Design/population	Follow-up period	Comparison group(s)	Definitions of groups	Findings
Reference group: Persistent smokers					
Sardari Nia et al. (2005)	• Prospective cohort • 321 patients with non-small cell lung cancer • 169 persistent smokers • 35 quitters • Belgium	• Every 4 months in Years 1 and 2 • Every 6 months in Year 3 • Annually from Years 4 to 6 through January 2003	• Quitters	• **Persistent smokers**: Patients who continued smoking (defined as current smokers in the study) • **Quitters**: Patients who had stopped smoking between the cancer diagnosis and the surgery. (1 week to more than 19 years)	• Persistent smokers: 1.0 (referent) • Quitters: unadjusted RR = 0.34 (95% CI, 0.16–0.71)
Chen et al. (2010)	• Retrospective cohort • 284 patients with limited-stage, small cell lung cancer • 76 persistent smokers • 87 quitters • Mayo Clinic	• At 6 months after diagnosis, then annually until December 2003	• Quitters	• **Persistent smokers**: Those who never quit smoking • **Quitters**: Those who had quit smoking at the time of or after the cancer diagnosis	• Persistent smokers: 1.0 (referent) • Quitters: adjusted HR = 0.55 (95% CI, 0.38–0.79)
Sandoval et al. (2009)	• Prospective cohort • 146 patients with oral cavity cancer • 101 patients who were current smokers at baseline • 30 persistent smokers at 1-year follow-up • 55 quitters Spain	• At 1 year and 2 years after diagnosis	• Quitters	• **Persistent smokers**: Those who were classified as current smokers at diagnosis of oral cancer and continued to smoke after the diagnosis • **Quitters**: Those who had quit smoking after the diagnosis, defined as quitting smoking at 1-year follow-up	• Persistent smokers: 1.0 (referent) • Quitters: unadjusted RR = 0.92 (95% CI, 0.46–1.84)

Table 4.9 Continued

Study	Design/population	Follow-up period	Comparison group(s)	Definitions of groups	Findings
Reference group: Quitters					
Tao et al. (2013)	• Prospective cohort Shanghai Cohort Study 1,632 male patients with cancer – 288 with lung cancer – 362 with stomach cancer – 248 with colorectal cancer – 107 with bladder cancer – 132 with prostate cancer – 492 with other cancer • 197 persistent smokers • 214 quitters	• Annually for 25 years through 2010	• Persistent smokers	• **Quitters**: Those who had quit smoking after a cancer diagnosis and remained quit throughout follow-up • **Persistent smokers**: Those who continued to smoke after a cancer diagnosis throughout follow-up	• Adjusted HR: – Quitters: 1.0 (referent) – Persistent smokers: 1.76 (95% CI, 1.37–2.27) • RR for quitters vs. persistent smokers: 0.568 (95% CI, 0.441–0.730)
Al-Mamgani et al. (2014)	• Retrospective cohort • 549 patients with T1a glottic cancer • 52 persistent smokers after radiotherapy • 215 quitters	• At the end of radiotherapy: – Weeks 4 and 6 – Months 3, 6, 12, 18, and 24 • Year 1: Every 2 months • Years 2 and 3: Every 3 months • Year 4 and beyond: Every 6 months	• Persistent smokers	• **Quitters**: Those who had stopped smoking after radiotherapy for T1a glottic cancer • **Persistent smokers**: Those who continued to smoke after radiotherapy for T1a glottic cancer	• Surviving percentage (not defined, but implied as 10-year survival): – Persistent smokers: 36% – Quitters: 70% ($p < 0.001$) • RR for quitters vs. persistent smokers: 0.190 (95% CI, 0.126–0.288, calculated)
Dobson Amato et al. (2015)	• Prospective cohort • 224 patients with lung cancer, all of whom were enrolled in a telephone-based tobacco treatment program • 129 persistent smokers at last follow-up • 95 quitters at last follow-up • Roswell Park Cancer Institute	• Survival duration was assessed in May 2014	• Persistent smokers	• **Quitters**: Those who reported having at least 24 hours' abstinence since the previous contact or follow-up assessment, or who had quit before the initial contact • **Persistent smokers**: Current smokers found at every contact not to have quit	• Adjusted HR: – Quitters: 1.0 (referent) – Persistent smokers: 1.79 (95% CI, 1.14–2.82) • RR for quitters vs. persistent smokers: 0.558 (95% CI, 0.355–0.877)

Table 4.9 Continued

Study	Design/population	Follow-up period	Comparison group(s)	Definitions of groups	Findings
Reference group: Quitters (continued)					
Roach et al. (2016)	• Retrospective cohort • 119 patients with lung cancer who were current smokers and treated with SBRT • 87 persistent smokers • 32 quitters	• Physical exam every 3 months for Years 1 and 2 • Chest CT scan every 3 months for Years 1 and 2, then every 6 months thereafter • Follow-up from 2004 to 2013	• Persistent smokers	• **Quitters**: Those who had quit smoking after SBRT • **Persistent smokers**: Those who smoked during and after SBRT	• Adjusted HR: – Quitters: 1.0 (referent) – Persistent smokers: 2.07 (95% CI, 1.02–4.2) • RR for quitters vs. persistent smokers: 0.483 (95% CI, 0.238–0.980)

Notes: **CI =** confidence interval; **CPS =** Cancer Prevention Study; **CT =** computed tomography; **HR =** hazard ratio; **RR =** risk ratio; **SBRT =** stereotactic body radiation therapy.

causal inference set out in the 1964 and 2004 Surgeon General's reports (U.S. Department of Health, Education, and Welfare 1964; USDHHS 2004).

Temporality

All studies evaluated the effects of smoking cessation after a cancer diagnosis. In all the studies, the temporal relationship was appropriate for causation because evaluation of smoking status, including smoking cessation, preceded the outcome of all-cause mortality.

Consistency

Six of the seven studies that directly compared smoking cessation with continued smoking observed significant improvements in all-cause mortality (Sardari Nia et al. 2005; Sandoval et al. 2009; Chen et al. 2010; Tao et al. 2013; Al-Mamgani et al. 2014; Dobson Amato et al. 2015). In the three studies that compared the risks of continued smoking or smoking cessation after a cancer diagnosis with never smoking, quitting smoking reduced risk compared with continued smoking (Yang et al. 2015a; Choi et al. 2016; Passarelli et al. 2016). The consistency of the observations extended across multiple types of cancer: head/neck, lung, breast, colorectal, bladder, and prostate. Observations spanned treatments with surgery, chemotherapy, or radiotherapy. Studies varied in geographic location and time span and in methodologic definitions for smoking status. Thus, in the broad range of the studies across cancer sites, treatments, and definitions of changes in smoking status, evidence consistently showed an improvement in all-cause mortality as a result of smoking cessation.

Strength of Association

The 2014 Surgeon General's report observed a 51% median increase in risk of all-cause mortality among cancer patients who were smokers compared with those who were never smokers (USDHHS 2014). For comparison, a review of 22 population-based cohorts from the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) found a doubled risk of all-cause mortality in current smokers and a 30% increased risk in former smokers compared with never smokers, reflecting an approximately 50% higher risk for current smokers compared with those who had quit smoking (Müezzinler et al. 2015). In the seven cohorts reviewed for this report that compared the effects of continued smoking and smoking cessation on all-cause mortality, the median relative risk of all-cause mortality was 1.82. Thus, with regard to all-cause mortality, the strength of the association between smoking and the reduction in risk for quitters is similar among cancer survivors and the general population.

Existing scientific evidence indicates that cancer patients substantially underreport their smoking: approximately 30% of patients who were smokers based on cotinine level reported themselves as nonsmokers (Khuri et al. 2001; Warren et al. 2012; Morales et al. 2013; Alberg et al. 2015). Thus, the associations between self-reported smoking and all-cause mortality, as reported in the 2014 Surgeon General's report, may be conservative.

Coherence

Smoking cessation at any age reduces all-cause mortality (USDHHS 2010, 2014; Thun et al. 2013b; Müezzinler et al. 2015). The adverse effects of smoking and the benefits of smoking cessation are well established for many diseases in the general population, including coronary heart disease, pulmonary disease, stroke, and other chronic health conditions. Smoking cessation reduces the risk of developing multiple types of cancer. Cigarette smoking by cancer patients increases all-cause mortality and cancer-specific mortality (USDHHS 2014). Much is known about the mechanisms by which smoking causes cancer (USDHHS 2010). Among these mechanisms, smoking appears to increase tumor progression. In experimental systems, constituents of cigarette smoke promote more aggressive phenotypes in cancer cells (Sobus and Warren 2014; Warren et al. 2014). A body of experimental evidence suggests that nicotine may promote all proliferation and tumor progression and increase risk for metastasis (Schaal and Chellappan 2014). Thus, smoking cessation among cancer patients would be anticipated to reduce all-cause mortality by reducing both noncancer-related mortality and cancer-related mortality. The 2014 Surgeon General's report identified a 51% median increased risk of all-cause mortality among cancer patients who smoked compared with cancer patients who quit smoking.

Synthesis of the Evidence

Ten studies in this section met the inclusion criteria, all including participants who were current smokers at the time of cancer diagnosis and who were evaluated for smoking cessation after diagnosis. The findings showed a benefit of cessation across a variety of cancer diagnoses and treatments. The magnitude of the observed associations is consistent with established reductions in all-cause mortality for smoking cessation in the general population. Given the relatively small body of evidence, limitations in the quality of the evidence, and the breadth of cancer

diagnoses and treatments, current evidence is suggestive but not sufficient to conclude that the observed reductions in all-cause mortality following smoking cessation generalize to all types of malignancies and modalities of treatment. The 2014 Surgeon General's report concluded that "quitting smoking improves the prognosis of cancer patients" (USDHHS 2014, p. 9). This cancer-specific conclusion contrasts with nonspecific, all-cause mortality, as considered above.

Conclusion

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking cessation and improved all-cause mortality in cancer patients who are current smokers at the time of a cancer diagnosis.

Implications

The evidence suggests that smoking cessation after a cancer diagnosis can significantly reduce all-cause mortality relative to continued smoking. This evidence is consistent with the known reduction in all-cause mortality due to smoking cessation in the general population. Thus, smoking cessation likely reduces all-cause mortality in cancer patients.

These conclusions strengthen the scientific basis for existing recommendations that emphasize the importance of quitting smoking after a cancer diagnosis. Many large national and international cancer organizations recommend addressing tobacco use among cancer patients. The American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research (AACR)—two of the largest clinical oncology and research organizations—maintain updated recommendations for addressing tobacco use in cancer patients. These organizations advocate for tobacco control, development of methods to facilitate smoking cessation, and practical approaches to enhance clinical care and research (AACR n.d.; ASCO n.d.). The International Association for the Study of Lung Cancer (IASLC) offers advanced recommendations for addressing tobacco use, particularly in the context of cancer care and lung cancer screening (IASLC n.d.). Recognizing the importance of addressing tobacco use and the lack of standardized approaches to screening, the National Cancer Institute (NCI) and the AACR developed standardized approaches for assessing tobacco use in clinical cancer research trials (Land et al. 2016). Similar standardized approaches to screening recommended by the NCI and AACR can also be applied to clinical care. Using these approaches, the National Comprehensive Cancer Network (NCCN) initiated the first series of recommendations to address tobacco use in all cancer patients who report having smoked during the past 30 days (NCCN n.d.). These guidelines follow the same format and approach as other clinical cancer guidelines, offering a resource to facilitate support for smoking cessation in a format that oncologists are familiar with. Although guidelines are available, they are not always implemented completely (Goldstein et al. 2013; Toll et al. 2013; Gritz et al. 2014; Gallaway et al. 2019), and tobacco treatment/cessation programs are not always offered in all cancer centers (Gallaway et al. 2019), suggesting a need to identify and address barriers to adoption of guidelines.

At present there is no standard format to promote smoking cessation in cancer patients. The context of addressing tobacco use in cancer patients is different from the context of addressing tobacco use in the general population of persons who do not have cancer because cancer patients are commonly presented with life-changing diagnoses and will regularly return for treatment for several months or years (Warren et al. 2014). The change in clinical care patterns associated with a new cancer diagnosis can affect frequency of follow-up with clinical providers and the perceived urgency of addressing tobacco use. Recognizing the clinical importance of tobacco use and tobacco cessation with the importance of developing approaches across a wide spectrum of clinical settings, NCI initiated in 2017 a Cancer Center Cessation Initiative (C3I) to fund the development of dedicated tobacco cessation approaches in 22 NCI Designated Cancer Centers (NCI 2018). In 2018, an additional 20 centers received funding at the same level (Croyle et al. 2019). Results from these centers are expected to help refine standardized approaches to screening for tobacco use and providing evidence-based support for smoking cessation. Furthermore, Warren and colleagues (2019) modeled the incremental costs due to failure of first-line cancer treatments because of continued smoking. Compared with nonsmokers, the attributable costs were estimated as $2.1 million per 1,000 patients or $10,700 per patient. These estimates strengthen the rationale for encouraging cessation among persons being treated for cancer.

The evidence reviewed in the 2014 Surgeon General's report documented the harm of smoking by persons with a cancer diagnosis, and this report builds on that finding by showing that such harm is reduced to some extent by smoking cessation. The conclusions of this report strengthen the rationale for aggressively promoting and supporting smoking cessation in cancer patients and survivors.

Cardiovascular Disease

Approximately 92.1 million American adults 20 years of age or older (more than 1 in 3 adults) have one or more types of cardiovascular disease (CVD), and by 2030 almost 44% of the population will have some form of CVD (Benjamin et al. 2017). In 2014, coronary heart disease (CHD) was listed on the death certificate for approximately 1 of every 7 deaths (Benjamin et al. 2017; National Center for Health Statistics 2017). The CVDs comprise some of the most common causes of death: CHD, congestive heart failure (CHF), cerebrovascular disease (including stroke), atherosclerosis (including aortic aneurysm), and hypertension. In the United States, CVD has accounted for more deaths since 1919 than any other major cause of death (Benjamin et al. 2019). CHD (43.2%) is the leading cause of death attributable to CVD, followed by stroke (16.9%), heart failure (9.3%), high blood pressure (9.8%), diseases of the arteries (3.0%), and other CVDs (Benjamin et al. 2019). In 2015, CVD was the leading cause (41.2%) of smoking-attributable age-standardized disability-adjusted life-years (DALYs), a combined indicator of smoking-attributable mortality and disease burden (GBD 2015 Tobacco Collaborators 2017). Since the first Surgeon General's report in 1964, the rates of age-adjusted CVD mortality have declined greatly; a reduction in smoking has been a major contributing factor to the decline in CHD mortality in particular (USDHHS 2014).

From 2014 to 2015, the average annual direct (medical) plus indirect costs of heart disease were estimated to total $218.7 billion (Benjamin et al. 2019). Heidenreich and colleagues (2011) projected that the direct (medical) cost of CHD in the United States would increase by approximately 200%, from $272.2 billion in 2010 to $818.1 billion in 2030.

Surgeon General's reports published since 1990 have not systematically covered the benefits of smoking cessation with regard to risk and outcomes for men and women with CVD. This section expands on previous reports by summarizing current knowledge of the effects of smoking cessation on risk of CVD and the natural history of this disease. This is not a systematic update, given the scope of the literature, and it does not cover all topics. Instead, this section provides examples of new findings that expand our understanding of conclusions from previous reports. Because of the wide range of research on this topic, this review focuses, where relevant, on summarizing results from meta-analyses or pooled analyses of findings from multiple cohorts and clinical trials.

Conclusions from Previous Surgeon General's Reports

The 1990 Surgeon General's report on the health benefits of smoking cessation (U.S. Department of Health and Human Services [USDHHS] 1990) provided several conclusions on smoking cessation and CVD (Table 4.10) that were updated in subsequent reports. Table 4.10 summarizes the major conclusions related to smoking cessation and CVD from the 1990, 2001, 2004, and 2010 Surgeon General's reports.

Literature Review Methods

For this Surgeon General's report, a literature review was conducted to update the cessation-specific findings from the 1990, 2001, 2004, 2006, 2010, and 2014 Surgeon General's reports. The search was restricted to English-language papers available on PubMed and published between January 2000 and August 31, 2017. Medical Subject Headings (MeSH) in PubMed were used to capture relevant articles. Retrieved articles included at least one term related to smoking cessation (e.g., "former smokers") and at least one term related to CVD (e.g., "coronary heart disease" [CHD]) or a term to describe the mechanism of disease (e.g., "thrombosis"). Citations from relevant retrieved articles and previous Surgeon General's reports and targeted searches were used to identify articles not captured by the search.

Relevant Mechanistic Data

Previous Surgeon General's reports have provided detailed reviews of potential mechanisms underlying how smoking and smoking cessation could affect the development of CVD (USDHHS 1983, 1990, 2004, 2006, 2010, 2014). This section reviews the links between smoking cessation and the following CVDs: CHD, cerebrovascular diseases, atrial fibrillation (AF), sudden cardiac death (SCD), heart failure, venous thromboembolism (VTE), lower-extremity peripheral artery disease (PAD), and abdominal aortic aneurysm (AAA). These diseases share some underlying mechanisms, and multiple risk factors contribute to each disease; for example, atherosclerosis and thrombosis are important for most of these diseases (International Agency for Research on Cancer [IARC] 2007).

Table 4.10 Conclusions from previous Surgeon General's reports on smoking cessation and cardiovascular disease

Year of report (page numbers)	Conclusions
USDHHS (1990, pp. 10–11)	1. Compared with continued smoking, smoking cessation substantially reduces risk of CHD among men and women of all ages. 2. The excess risk of CHD caused by smoking is reduced by about half after 1 year of smoking abstinence and then declines gradually. After 15 years of abstinence, the risk of CHD is similar to that of persons who have never smoked. 3. Among persons with diagnosed CHD, smoking cessation markedly reduces the risk of recurrent infarction and cardiovascular death. In many studies, this reduction in risk of recurrence or premature death has been 50% or more. 4. Smoking cessation substantially reduces the risk of peripheral artery occlusive disease compared with continued smoking. 5. Among patients with peripheral artery disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival. 6. Smoking cessation reduces the risk of both ischemic stroke and subarachnoid hemorrhage compared with continued smoking. After smoking cessation, the risk of stroke returns to the level of never smokers; in some studies this has occurred within 5 years, but in others as long as 15 years of abstinence were required.
USDHHS (2001, pp. 13–14)	1. The risk for coronary heart disease among women is substantially reduced within 1 or 2 years of smoking cessation. This immediate benefit is followed by a continuing but more gradual reduction in risk to that among nonsmokers by 10 to 15 or more years after cessation. 2. In most studies that include women, the increased risk for stroke associated with smoking is reversible after smoking cessation; after 5 to 15 years of abstinence, the risk approaches that of women who have never smoked. 3. Smoking is a strong predictor of the progression and severity of carotid atherosclerosis among women. Smoking cessation appears to slow the rate of progression of carotid atherosclerosis. 4. Women who are current smokers have an increased risk for peripheral vascular atherosclerosis. Smoking cessation is associated with improvements in symptoms, prognosis, and survival.
USDHHS (2004, p. 25)	1. Quitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general.
USDHHS (2010, p. 11)	1. Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with or without coronary heart disease. 2. The use of nicotine or other medications to facilitate smoking cessation in people with known cardiovascular disease produces far less risk than the risk of continued smoking.

Notes: **CHD =** coronary heart disease.

Atherosclerosis is the key underlying pathophysiologic process leading to most clinical manifestations of CVD, including CHD, cerebrovascular disease, and PAD. Atherosclerosis involves the hardening and narrowing of arteries because of deposition of lipids in the inner layers of arteries, fibrosis, and thickening of the arterial wall. This complex process involves the deposition of lipids, inflammatory and immune responses to oxidized lipids, and endothelial dysfunction. When the processes involved in atherosclerosis culminate in thrombosis, this can lead to myocardial infarction (MI) or ischemic stroke (Nagareddy and Smyth 2013).

Key mechanisms through which smoking and smoking cessation affect atherogenesis and thrombosis include endothelial function and injury, oxidative stress, hemostatic factors (platelet function, fibrinogen, and d-dimer), fibrinolysis, inflammation, lipid modification, and vasomotor function (IARC 2007). Smoking and smoking cessation may also influence CVD risk through the effect of oxygen demand and supply on cardiovascular function (USDHHS 2004) and through effects on occurrence of arrhythmias and coronary artery spasm (USDHHS 1990).

The 1990 Surgeon General's report focused primarily on how smoking affects or may affect mechanisms leading to CVD and described mechanisms that could come into play when smokers quit (USDHHS 1990). The report concluded that some CVD effects of smoking appeared to be reversed within days or weeks of quitting (e.g., increased platelet activation, changes in clotting factors, level of carboxyhemoglobin, occurrence of coronary artery spasm and ventricular arrhythmias), but that other effects (e.g., advance of atherosclerosis, proliferation of smooth

muscle cells, lipid deposition) may be irreversible or only slowly reversible.

The 2004 Surgeon General's report provided a detailed overview of mechanisms linking smoking with CVD development. That report concluded that smoking (1) promotes endothelial injury and cell dysfunction; (2) produces a substantial shift in hemostatic balance at the endothelium, leading to atherosclerosis and thrombotic complications; (3) diminishes the ability of the blood to carry oxygen; and (4) increases physiologic demands of the myocardium (USDHHS 2004). Through these mechanisms, smoking results in substantial adverse alterations in the cardiovascular system's hemostatic balance, explaining the relationship between smoking and the subclinical and clinical manifestations of atherosclerosis. The 2010 Surgeon General's report reviewed in detail the mechanisms through which cigarette smoking causes CHD (USDHHS 2010), concluding that smoking produces insulin resistance that could, in tandem with chronic inflammation, accelerate the development of macrovascular and microvascular complications, such as nephropathy.

The 2014 Surgeon General's report expanded on the research related to the mechanisms through which cigarette smoking affects cardiovascular function, focusing on how smoking affects atherogenesis, endothelial function, thrombosis, and inflammation (USDHHS 2014). The year before, Csordas and Bernard (2013) reviewed the biology of the atherothrombotic effects of smoking. Elsewhere, Messner and Bernhard (2014) reviewed how smoking causes endothelial dysfunction and initiates atherogenesis. The next sections highlight some of the findings related to mechanisms through which smoking cessation could alter the development and progression of CVD.

Mechanisms Through Which Smoking Cessation Could Affect Cardiovascular Disease

As described in the 2010 Surgeon General's report, there are multiple mechanisms by which cigarette smoking contributes to acute cardiovascular events and increases the risk for developing CVDs over the long term (USDHHS 2010). Smoking cessation terminates exposure to the constituents and metabolites in tobacco smoke that drive some of these mechanisms, leading to both rapid and more delayed reduction of risk.

Carbon Monoxide and Nicotine

Several specific components of cigarette smoke are directly relevant to the benefits of smoking cessation: carbon monoxide (CO), nicotine, and oxidant gases, which contribute to inflammation. Tobacco smoke contains high concentrations of CO, which is a gas (USDHHS 2010). The mechanisms by which CO may contribute to acute cardiovascular events are well characterized. CO binds to hemoglobin, reducing oxygen-carrying capacity, and also shifts the oxyhemoglobin desaturation curve so that less oxygen is released to tissues from hemoglobin. The half-life of CO is brief: smoking-related CO in the body is cleared within several days of cessation (USDHHS 2010).

Nicotine is pharmacologically active and sympathomimetic in its action, causing release of catecholamines from the neurons and from the adrenal gland. This release of catecholamines transiently increases heart rate and blood pressure and results in vasoconstriction, which can contribute to myocardial hypoxia and, hence, increase risk for acute cardiovascular events. Successful smoking cessation ends exposure to nicotine and provides an immediate benefit in terms of reducing risk for acute cardiac events.

Hemodynamic Effects

Smoking impairs vascular endothelial function and activates the sympathetic nervous system. In combination with underlying atherosclerosis, these hemodynamic consequences of smoking increase the risk for CVD events. Alterations in vasomotor function because of smoking appear to be substantially reversible, suggesting the important role that smoking cessation and smokefree environments can play in reducing the burden of CVDs (USDHHS 2010).

Endothelial Effects

The endothelium plays a role in vascular tone, growth, thrombogenicity, and inflammation (Lerman and Zeiher 2005). Dysfunction and injury of the endothelium affects atherogenesis initiation and the development of acute CVD events, and endothelial dysfunction is an independent risk factor for CVD morbidity and mortality (USDHHS 2010). Smoking may impair regeneration of the endothelium; however, 2–4 weeks of cessation has been associated with increases in the number of progenitor cells, which is indicative of repair of the endothelium (Kondo et al. 2004).

Both active smoking and exposure to secondhand smoke can alter coronary and peripheral arterial vasomotion among persons with or without CHD (Czernin and Waldherr 2003). Correspondingly, evidence suggests that smoking cessation can improve endothelial functioning. Smoking cessation leads to improved endothelial-dependent vasodilation in veins in the human hand within 24 hours of cessation (Moreno Jr et al. 1998). Reduced altered brachial artery flow-mediated dilation (FMD) is an early marker for endothelial dysfunction and a risk factor for CVD. Smoking is associated with reduced FMD. This relationship is dose related and may be reversible, as a weaker association has been observed in former smokers

(Celermajer et al. 1993; Raitakari et al. 1999). Johnson and colleagues (2010) reported on a clinical trial that assessed smoking cessation pharmacotherapies in 1,504 smokers; among the 36% of participants who quit smoking, FMD increased by 1% (from 6.2% +/- 4.4% to 7.2% +/- 4.2%) after 1 year—a relative gain of approximately 15%. In contrast, FMD did not change among those who continued to smoke. Results were similar after adjusting for artery diameter, reactive hyperemia, low-density lipoprotein cholesterol, and the presence of a smokefree rule in the home.

In another study, smoking "light" cigarettes (a type of cigarette that was claimed by manufacturers to produce less tobacco tar than a regular cigarette when smoked) was not associated with improved FMD relative to smoking regular cigarettes, providing evidence that "light" cigarettes are not a less harmful alternative to higher yield cigarettes for reducing CVD risk (Amato et al. 2013). In cross-sectional adjusted analyses of data from the Bogalusa Heart Study, former cigarette smokers, compared with current smokers, had higher small-artery compliance, as estimated by radial artery pressure pulse contour analysis, and decreased systemic vascular resistance, with a trend of improvement with increased time since cessation (Li et al. 2006). In the U.S.-based Multi-Ethnic Study of Atherosclerosis (MESA), McEvoy and colleagues (2015b) did not find consistent associations between smoking status (current, former, or never) and measures of vascular dynamics and function (carotid distensibility, aortic distensibility, or FMD). In addition, time since cessation was not associated with these outcomes, possibly because of the older ages of the participants.

Studies have also found that smoking cessation is associated with changes in biomarkers of endothelial function, dysfunction, or activation. In an intervention study focused on lifestyle changes in young adults with family histories of premature CHD, those who quit smoking had significantly lower concentrations of intercellular adhesion molecule-1 (ICAM-1), a biomarker of endothelial activation, compared with those continuing to smoke (Tonstad et al. 2005). Elsewhere, in a small study of a smoking cessation intervention among persons at high risk of CVD, ICAM-1 decreased among quitters after 1 year of cessation but increased among persons who continued to smoke (Halvorsen et al. 2007). Other markers related to endothelial function, thrombotic state, or inflammation (E-selectin, interleukin 6, sCD40 ligand, tumor necrosis factor a, von Willebrand factor, and C-reactive protein [CRP]) did not change during the study period. In a small study of young, healthy smokers, coronary vasomotor abnormality appeared to improve after 1 month of smoking cessation (Morita et al. 2006). Later, Huang and colleagues (2016) examined two Swedish cohorts to assess the relationships of smoking with 80 protein markers known to be related to CVD risk. In replication analyses, current cigarette smoking was associated with 10 proteins representing endothelial dysfunction, inflammation, neointimal formation, foam cell formation, and plaque instability (Huang et al. 2016). Among former smokers, no consistent associations were observed.

A systematic review of the literature concluded that the evidence was uncertain as to whether smoking cessation leads to a reversal in arterial stiffness (Doonan et al. 2010). In the Atherosclerosis Risk in Communities (ARIC) study of older adults, among women, femoral-ankle pulse wave velocity, a measure of arterial stiffness, was lower in current smokers and former smokers than in never smokers, and lower in former smokers than in current smokers (Camplain et al. 2016). Among women, both smoking status and cumulative smoking exposure were associated with lower peripheral arterial stiffness. Among men, this study did not find a relationship between smoking cessation and a reversal in arterial stiffness, and it did not reveal an association with time since smoking cessation or with carotid-femoral pulse wave velocity.

Thrombogenic Effects

The 2010 Surgeon General's report noted that smoking-mediated thrombosis appears to be a major factor in the pathogenesis of acute cardiovascular events and described how smoking leads to alterations in the blood and in the blood vessels that promote thrombosis, a pathologic reaction that can result in smoking-related MI or stroke (USDHHS 2010). The report summarized how the hypercoagulable state associated with both active smoking and exposure to secondhand smoke is evident in the epidemiology of related cardiovascular events and in the rapid decline in risk of such events after smoking cessation (USDHHS 2010).

In cross-sectional analyses of 19,600 participants from the Third National Health and Nutrition Examination Survey (NHANES III, conducted from 1988 to 1994), cigarette smoking was strongly and positively associated with elevated levels of fibrinogen and homocysteine, which are markers of a hypercoagulable state (fibrinogen is also a marker of inflammation) (Bazzano et al. 2003). In addition, there was a dose-response relationship with these markers. Compared with never smokers, former smokers (median of 10 years since cessation) had higher odds of elevated fibrinogen but not of elevated homocysteine. Additionally, current smokers had higher odds of elevated fibrinogen compared with former smokers. Further analyses of data from the NHANES III showed a trend of lower levels of fibrinogen with increasing time since smoking cessation: After approximately 5 years of cessation, levels were similar to those of never smokers (Bakhru and Erlinger 2005).

Among 174 smokers who underwent an intensive 12-month smoking cessation program, levels of von Willebrand factor (a marker of circulating endothelial-coagulative activation) decreased significantly 2, 6, and 12 months after smoking cessation compared with baseline among those who maintained cessation at each follow-up (Caponnetto et al. 2011). In those who quit smoking, concentrations of d-dimer, prothrombin fragment 1 + 2, platelet factor-4, and β-thromboglobulin (all markers of circulating endothelial-coagulative activation) were significantly lower 6 and 12 months after cessation compared with baseline. In a nicotine replacement therapy trial among 197 men, those who quit smoking had improved plasma fibrinogen, reactive capillary flow, and transcutaneous partial oxygen tension (three parameters of blood flow) after 6 months of cessation compared with levels measured at baseline (Haustein et al. 2002). Hematocrit levels and white blood cell counts were lower in quitters compared with those who relapsed; this suggests decreased inflammation in these individuals, as white blood cells play an important role in the inflammatory process. Changes in plasma viscosity and erythrocyte deformability were inconclusive.

Other studies have also found that circulating levels of fibrinogen are higher in smokers and decrease with cessation, with one study finding a decreased rate of fibrinogen synthesis and lower plasma fibrinogen concentrations just 2 weeks after cessation (Hunter et al. 2001). Blann and colleagues (1997) found decreases in many hematologic and coagulation indices in former smokers who used nicotine gum or patches to quit smoking; there were few additional changes after the participants no longer used any nicotine replacement products. Lúdvíksdóttir and colleagues (1999) observed similar results for atherogenic and thrombogenic factors in a smoking cessation trial involving a nicotine nasal spray versus placebo.

Inflammation

Research suggests that smoking leads to a chronic inflammatory state, activates monocytes, and enhances the recruitment and adhesion of leukocytes to blood vessel walls, an important step in vascular inflammation (USDHHS 2010). Evidence indicates that vascular inflammation, in turn, appears to play a role in atherogenesis; and markers of inflammation, such as CRP, predict the risk of future CVD events (Libby et al. 2002).

Several studies have explored the relationships between smoking and markers of inflammation, such as CRP (Bermudez et al. 2002; Bazzano et al. 2003; Bakhru and Erlinger 2005; Helmersson et al. 2005; Ohsawa et al. 2005; Madsen et al. 2007; Hastie et al. 2008; Levitzky et al. 2008; Lao et al. 2009; Reichert et al. 2009; Asthana et al. 2010; Zatu et al. 2011; Golzarand et al. 2012; Marano et al. 2015; McEvoy et al. 2015b; Kianoush et al. 2017; King et al. 2017). In most of these studies, current and former smokers had higher levels of inflammatory markers than nonsmokers (Bermudez et al. 2002; Bazzano et al. 2003; Helmersson et al. 2005; Madsen et al. 2007; Hastie et al. 2008; Levitzky et al. 2008; Lao et al. 2009; Golzarand et al. 2012; Marano et al. 2015; McEvoy et al. 2015b; Kianoush et al. 2017), and in five of the studies inflammatory levels decreased in former smokers with increasing time since smoking cessation (Bakhru and Erlinger 2005; Ohsawa et al. 2005; Reichert et al. 2009; McEvoy et al. 2015b; Kianoush et al. 2017).

In the cross-sectional analyses of data from NHANES III (described previously), cigarette smoking was independently and positively associated with elevated levels of CRP, and there was a dose-response relationship (Bazzano et al. 2003). In analyses of the odds of having either a detectable CRP or a clinically elevated CRP level, former smokers had higher odds compared with never smokers but lower odds compared with current smokers. Additional analyses showed a trend of decreasing white blood cell counts and clinically detectable CRP with increased time since smoking cessation: Approximately 5 years after cessation, white blood cell counts and the odds of detectable CRP did not differ significantly from those of never smokers (Bakhru and Erlinger 2005).

In the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), among 4,121 former smokers, time since cessation was inversely related to levels of high-sensitivity CRP (Kianoush et al. 2017). Similarly, in the U.S.-based MESA cohort, levels of high-sensitivity CRP were higher in current smokers than in former smokers, and levels of high-sensitivity CRP decreased with increased time since cessation (McEvoy et al. 2015b). Notably, this study used cotinine to classify smoking status. In a cross-sectional study by Hastie and colleagues (2008), levels of CRP were similar in never and former smokers approximately 5 years after cessation. In that study, extent of lifetime smoking (assessed by number of pack-years) was a predictor of levels of CRP after smoking cessation, independent of time since cessation, suggesting that levels of CRP may be higher in smokers because of a secondary effect, such as tissue damage caused by inflammation.

In observational analyses of 1,504 smokers enrolled in a smoking cessation trial in which 36% of participants had abstained for 1 year, smoking cessation was not associated with level of CRP (Asthana et al. 2010). There was also no relationship of smoking intensity to CRP, although smoking intensity was associated with increased white blood cell counts. The authors suggested that the effects of adiposity on levels of CRP may have masked the relationship between smoking and CRP. A study by King and colleagues (2017) of 1,652 smokers attempting to quit

examined six inflammatory markers of CVD risk: CRP, D-dimer, fibrinogen, urinary F2 isoprostane:creatinine (F2:Cr) ratio, white blood cell count, and myeloperoxidase. After 1 year, 21% of participants had successfully quit. Cessation was associated with an improved F2:Cr ratio and decreased white blood cell counts independent of weight change but not with other inflammatory markers. Smoking intensity was associated with the F2:Cr ratio, myeloperoxidase, and white blood cell counts. The authors concluded that smoking cessation may have led to reduced inflammation by lowering oxidative stress.

Lipid Abnormalities

Cigarette smoking is associated with lipid profiles that are likely to contribute to the development of atherosclerosis and CVD risk, a topic reviewed in depth in the 2010 Surgeon General's report (USDHHS 2010). Much evidence supports the conclusion that smoking is associated with higher levels of triglycerides (which in turn are associated with levels of very-low-density lipoproteins, total triglycerides, and apolipoprotein B [APO B]), with modestly higher levels of low-density lipoproteins cholesterol (LDL-C), and with lower levels of plasma high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (APO A-I) (USDHHS 2010). The 2010 Surgeon General's report also found that plasma lipid and lipoprotein levels among former cigarette smokers were typically similar to those of nonsmokers.

In a meta-analysis of articles published from 1966 to 2000, Maeda and colleagues (2003) concluded that, based on analyses from 27 prospective studies, smoking cessation is associated with beneficial increases in HDL-C. In this analysis, changes in the levels of total cholesterol, LDL-C, and triglycerides were not significant. Later, Forey and colleagues (2013), in a meta-analysis of 45 studies, found that levels of HDL-C increased rapidly (within weeks) after cessation, but there was no clear pattern after that time.

In a study conducted by Gepner and colleagues (2011), a clinical trial of cessation pharmacotherapies in 1,504 smokers that was included in the meta-analysis by Forey and colleagues (2013), those who successfully quit (36% of participants) had, at 1-year follow-up, higher levels of HDL-C, total HDL, and large HDL particles compared with baseline. Smoking cessation was not, however, associated with changes in LDL-C or LDL size. These results were similar to those reported in the meta-analysis by Maeda and colleagues (2003). Importantly, smokers in the study by Gepner and colleagues (2011) generally had a higher body mass index (BMI) than those in previous studies and thus were more representative of the contemporary U.S. population. Elsewhere, in two reports based on a study in which participants were on the nicotine patch for 32 days and then taken off it for 45 days, HDL-C levels did not increase significantly among former smokers on the patch, but those levels increased quickly after they stopped using the patch (Moffatt et al. 2000; Chelland Campbell et al. 2008). Of note, nicotine products were used in some arms of the trial by Gepner and colleagues (2011), but that trial did observe higher levels of total HDL at 1-year follow-up.

Summary of the Evidence

Substantial evidence shows that smoking cessation is associated with an improvement in many pathogenetic factors involved in processes through which cigarette smoking causes CVD. Some effects appear to be rapidly reversible with smoking cessation, but other effects may reverse much more slowly or not at all. Evidence indicates that smoking cessation (1) leads to a reduction in markers of inflammation and hypercoagulability and to rapid changes in levels of HDL-C in a favorable direction and (2) may lead to improved endothelial function.

Smoking Cessation and Subclinical Atherosclerosis

According to the 2004 Surgeon General's report, the evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis (USDHHS 2004). That report addressed the implications of this conclusion, finding that cigarette smoking has a causal relationship with the full natural history of atherosclerosis—from the early stages that are detected by subclinical markers to the late, often fatal, stages. Findings presented at that time indicated the potential for smoking cessation (including quitting and then maintaining cessation) to prevent more advanced, clinically symptomatic disease.

The 2001 Surgeon General's report concluded that smoking is a strong predictor of the progression and severity of carotid atherosclerosis among women and that smoking cessation appears to slow the rate at which carotid atherosclerosis progresses (USDHHS 2001). Since this report appeared, additional approaches have been developed to measure subclinical atherosclerosis, and more evidence has been published indicating that smoking cessation can slow the progression of atherosclerosis.

As described in the 2004 Surgeon General's report, examining measures of subclinical atherosclerosis facilitates assessment of the relationship between smoking and the earlier, preclinical stages of the atherosclerotic disease process. In studies of subclinical measures among healthy persons, findings may be less susceptible to reverse causation, as there is no onset of symptoms that could lead to cessation and distort the temporal relationship between

smoking and CVD. The possibility of reverse causation (for clinical and subclinical outcomes) is of particular concern for cross-sectional analyses in which it may not be possible to ascertain temporality.

Table 4.11 describes findings from 12 studies that have assessed the relationships between smoking cessation and subclinical atherosclerosis (Kiechl et al. 2002; Baldassarre et al. 2009; Jöckel et al. 2009; Liang et al. 2009; Jiang et al. 2010; Kweon et al. 2012; Lehmann et al. 2014; McEvoy et al. 2015b; Yang et al. 2015b; Hansen et al. 2016; Hisamatsu et al. 2016; Kianoush et al. 2017). Studies in many different populations have found, generally, that smoking is positively associated with the presence, extent, and progression of atherosclerosis measured in different vascular beds. Compared with never cigarette smokers, both current and former smokers tend to have more extensive atherosclerosis, although former smokers generally have less extensive atherosclerosis than current smokers. Studies in other populations and studies of other markers for atherosclerosis have reported similar findings (Fowkes et al. 2013; Yi et al. 2015; Pacheco et al. 2016). Time since smoking cessation is also related to the extent of atherosclerosis, with less atherosclerotic burden as time since cessation increases (Jiang et al. 2010; Kweon et al. 2012; McEvoy et al. 2015b; Hansen et al. 2016; Hisamatsu et al. 2016; Kianoush et al. 2017).

Hansen and colleagues (2016) conducted one of several studies assessing the relationship between smoking cessation and the progression of atherosclerosis. This study examined a subcohort of the prospective Malmö Diet and Cancer study in Sweden and found that, compared with never smokers, former smokers had an adjusted difference in the yearly progression rate of 0.0074 millimeters (mm) per year (95% confidence interval [CI], 0.0018–0.0129) in maximal intimal-media thickness (IMT) in the carotid bifurcation (Table 4.11). But compared with never smokers, moderate smokers had an adjusted difference of 0.0106 mm (95% CI, 0.0038–0.0175) and heavy smokers had an adjusted difference of 0.0146 mm (95% CI, 0.0016–0.0230). Among former smokers, as time since smoking cessation increased, there was a reduction in yearly progression of IMT in the carotid bifurcation and in the rate of lumen reduction, with a distinct lowering in progression rates more than 5 years after cessation. In a study of 127 smokers in the Netherlands, successful smoking cessation for 2 years did not result in slowing of the increase in carotid IMT or a reduction in the thickening of the carotid artery, a finding potentially attributable to the study's small size and relatively short follow-up (data not shown in table) (van den Berkmortel et al. 2004). Carotid IMT is a predictor of future CVD events (Lorenz et al. 2007), although its measurement may have no added value for predicting cardiovascular risk (Den Ruijter et al. 2012).

Results from cross-sectional analyses in 2000–2003 of the Heinz Nixdorf Recall Study in Germany were used to estimate the slowing by cessation of coronary artery calcification (CAC), compared with continued smoking (Table 4.11). Compared with continued smoking, smoking cessation at 45, 55, and 65 years of age was estimated to slow CAC progression at 75 years of age by 9, 6, and 3 years, respectively (Jöckel et al. 2009). CAC is a predictor of future CVD events (Pletcher et al. 2004; Chaikriangkrai et al. 2017). Although the findings from Jöckel and colleagues (2009) were based on modeling assumptions and cross-sectional data, their results suggest that smoking cessation may reduce the progression of atherosclerosis, which could potentially reduce the risk of future clinical CVD.

Several studies (Table 4.11) have assessed associations between smoking and the ankle-brachial index (ABI), which is also known as the ankle-arm index (McEvoy et al. 2015b; Hisamatsu et al. 2016; Kianoush et al. 2017). The ABI is the ratio of blood pressure in the lower leg to that in the upper arm. A low ABI is associated with an increased risk of CHD and of CVD (Lin et al. 2013). The ABI has been used as a way to assess the presence of PAD, but it does not assess which blood vessels are narrow or blocked. In two studies (Table 4.11), former smoking was associated with higher odds of a low ABI compared with never smoking (McEvoy et al. 2015b; Kianoush et al. 2017), and in three studies, increased time since quitting was associated with lower odds of having a low ABI (McEvoy et al. 2015b; Hisamatsu et al. 2016; Kianoush et al. 2017). For example, in the MESA cohort, the odds ratio (OR) for an ABI <1.0 was 0.91 (95% CI, 0.86–0.96) for every 5-year increment since smoking cessation (McEvoy et al. 2015b). The relationship between smoking cessation and clinical manifestations of PAD is discussed in more detail in a later section.

Summary of the Evidence

Evidence indicates that smoking cessation reduces the development and progression of markers of subclinical atherosclerosis, with the degree of reduction increasing as time since cessation increases. This pattern of change in markers provides mechanistic background on the evidence of how smoking cessation reduces risk of CVD.

Smoking Cessation and Cardiovascular Disease

The 2010 Surgeon General's report concluded that smoking cessation reduces the risk of cardiovascular morbidity and mortality for cigarette smokers with or without CHD (USDHHS 2010). This report also found that there

Table 4.11 Studies on the association between smoking cessation and subclinical atherosclerosis

Study	Design/population	Main results	Comments
Kiechl et al. (2002)	• Prospective cohort (Bruneck Study) • 826 healthy or sick participants, 40–79 years of age, 50% men, 26% former smokers • 1990–1995 • Italy • Follow-up: 5 years • Outcome: carotid IMT, early atherogenesis (nonstenotic plaques), advanced atherogenesis (stenosis >40%)	• Current and former smokers had increased risk of early atherogenesis only if they had chronic infections; risks were similar in never, former, and current smokers without chronic infection • Advanced atherogenesis developed independently of chronic infection; risk returned to normal soon after cessation	Impact of smoking on atherosclerosis appears to be partially mediated by chronic infections
Baldassarre et al. (2009)	• Cross-sectional study • 1,804 consecutive patients' first visit to lipid clinic, 21–85 years of age, 48% men, 21% former smokers • 2000–2003 • Italy • Outcome: carotid IMT (mean, total, and maximum)	• Carotid IMT was highest in current smokers, then former smokers, then never smokers • Only after adjusting for risk factors was carotid IMT significantly higher among current smokers than former smokers • Carotid IMT was positively associated with pack-years of smoking among both former and current smokers	Results may not be generalizable to populations without dyslipidemi
Liang et al. (2009)	• Cross-sectional and prospective analyses (Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology) • 1,132 participants, 35–64 years of age; 34% men; 3% former smokers at baseline; free of myocardial infarction, stroke, and diabetes • Scanned in 1993–1994 and 2002 • China • Exposure: smoking status at baseline and consistency during follow-up • Outcome: mean common carotid IMT	• Mean adjusted IMT was 0.72 mm for consistent current smokers, 0.71 mm for former and inconsistent smokers, and 0.70 mm for consistent never smokers (p for trend <0.01) • Compared with consistent never smokers, consistent current smokers had higher adjusted odds of carotid plaques; a similar pattern was observed among former smokers and former/inconsistent smokers, but the results were not significant	—
Jöckel et al. (2009)	• Cross-sectional study (Heinz Nixdorf Recall Study) • 4,078 participants, 45–75 years of age, 50% men, without manifest CHD (myocardial infarction or coronary revascularization) or stroke • Scanned in 2000–2003 • Germany • Outcome: CAC	• Smoking cessation at 45, 55, or 65 years of age was associated with CAC at the age of 75 years that would have been reached 9, 6, or 3 years earlier, respectively, had smoking continued • CAC accumulation slowed after cessation, but advanced CAC persisted for a long time	Results are based on predictions from regression models run separately by smoking status; models were not run separately for men and women

Table 4.11 Continued

Study	Design/population	Main results	Comments
Jiang et al. (2010)	• Cross-sectional study • 959 men, 50–85 years of age, 26% former smokers • Scanned in 2006–2007 • China • Outcome: mean common carotid IMT, presence of CCA plaques; CCA atherosclerosis defined as CCA-IMT ≥1.0 mm or with a stenosis diameter ≥20%	• IMT and number of plaques increased from never, to former, to current smokers • Longer duration since cessation was associated with decreased odds of the presence and severity of atherosclerosis in CCA (explored in categories of 1–9, 10–19, ≥20 years since cessation; observed benefit compared with current smokers for ≥10 years since quitting)	—
Kweon et al. (2012)	• Cross-sectional study (Dong-gu Study) • 2,503 men, ≥50 years of age, 51% former smokers • Scanned in 2007–2009 • Korea • Outcome: CCA-IMT, carotid plaque, CCA diameter	• Compared with never smokers, current smokers had greater CCA IMT, CCA diameter, and odds of carotid plaque • Among former smokers, CCA IMT and CCA diameter decreased with years since cessation; not observed for carotid plaque • For current smokers, but not for former smokers, a dose-response relationship was observed between pack-years of smoking and CCA IMT	Only men were included in analysis because of a very low prevalence of smoking among women
Lehmann et al. (2014)	• Prospective study (Heinz Nixdorf Recall Study) • 1,261 participants, 45–75 years of age, 27% men, no detectable CAC at first scan, no history of CHD or stroke • Scanned in 2000–2003, rescanned 5 years later • Germany • Outcome: onset of detectable CAC	• Compared with never smokers, onset of detectable CAC occurred approximately 10 years earlier among current smokers and 5 years earlier among former smokers • Among women, in adjusted analyses, current smokers had higher odds of progression to detectable CAC than never smokers; no association for former smokers • Among men, smoking was not related to CAC onset	Unclear whether there was adjustment for other factors in the analysis of time to detectable CAC

Table 4.11 Continued

Study	Design/population	Main results	Comments
McEvoy et al. (2015b)	• Cross-sectional study (Multi-Ethnic Study of Atherosclerosis) • 6,796 multiethnic participants, 45–84 years of age, 47% men, 38% former smokers, free of CVD • 2000–2002 • United States (six centers) • Outcomes: mean internal carotid IMT, CAC, and ABI	• Difference in log (IMT)a (95% CI): • Never smoker: 0.00 (referent) – Former smoker: 0.05 (0.03–0.07) – Current smoker: 0.09 (0.06–0.12) • Odds ratio of CAC >0 (95% CI): • Never smoker: 1.00 (referent) – Former smoker: 1.28 (1.21–1.57) – Current smoker: 1.79 (1.49–2.14) • Odds ratio of CAC >75th percentile (95% CI): • Never smoker: 1.00 (referent) – Former smoker: 1.18 (0.99–1.41) – Current smoker: 1.38 (1.08–1.77) • Odds ratio of ABI <1 (95% CI): • Never smoker: 1.00 (referent) – Former smoker: 1.24 (1.02–1.50) – Current smoker: 2.22 (1.74–2.83) • Time since quitting was independently associated with atherosclerosis; for example, OR of CAC >0 was 0.94 (95% CI, 0.90–0.97) for each 5 years since quitting	—
Yang et al. (2015b)	• Cross-sectional study (Northern Manhattan Study) • 1,743 multiethnic participants, ≥39 years of age, 40% men, 38% former smokers, free of stroke • Years of data collection: not provided • New York, New York (northern Manhattan) • Outcome: carotid plaque echodensity divided into quintiles	• Compared with never smokers, current smokers were more likely to have soft or calcified plaques • Compared with never smokers, former smokers were more likely to have echodense plaques	More research is needed to understand whether plaque morphology mediates the relationship between smoking and clinical CVD

Table 4.11 Continued

Study	Design/population	Main results	Comments
Hansen et al. (2016)	• Prospective cohort (Malmö Diet and Cancer cardiovascular cohort) • 2,992 middle-aged participants, 41% men, 35% former smokers, free of CVD • 1991–1994 baseline and 2007–2012 visit (subcohort of those born 1926–1945) • Sweden • Outcomes: mean common carotid IMT and maximum carotid bifurcation, degree of lumen diameter reduction	• Difference in IMT progression (mm/year) (95% CI): – CCA: ○ Never smoker, unexposed to secondhand smoke: 1.00 (referent) ○ Former smoker: 0.0014 (0.0001–0.0028) ○ Moderate smoker (1–15 cigarettes smoked per day): 0.0027 (0.0010–0.0044) ○ Heavy smoker (>15 cigarettes smoked per day): 0.0041 (0.0020–0.0062) – Carotid bifurcation: ○ Never smoker, unexposed to secondhand smoke: 1.00 (referent) ○ Former smoker: 0.0074 (0.0018–0.0129) ○ Moderate smoker: 0.0106 (0.0038–0.0175) ○ Heavy smoker: 0.0146 (0.0061–0.0230) • Differences in rate of diameter reduction (%/year) (95% CI): – Never smoker, unexposed to secondhand smoke: 1.00 (referent) – Former smoker: 0.25 (0.001–0.36) – Moderate smoker: 0.25 (0.11–0.38) – Heavy smoker: 0.43 (0.26–0.59) • Stronger associations for current smokers • With >5 years since cessation, rate of IMT bifurcation progression decreased; similar pattern for lumen reduction	Similar results when adjusted for inflammatory markers

Table 4.11 Continued

Study	Design/population	Main results	Comments
Hisamatsu et al. (2016)	• Cross-sectional study (Shiga Epidemiological Study of Subclinical Atherosclerosis) • 1,019 Japanese men, 40–79 years of age, 50% former smokers, free of CVD • 2006–2008 • Japan • Outcomes: ABI <1.1; mean carotid IMT; AoAC and CAC	• Former smoking was associated with higher carotid IMT (IMT >1.0 mm, OR = 1.94 [95% CI, 1.13–3.34]) and AoAC (AoAC >0, OR = 2.55 [95% CI, 1.45–4.49]) compared to never smokers • Current smoking was positively associated with all four outcomes: – CAC >0, OR = 1.79 (95% CI, 1.16–2.79) – Carotid IMT >1.0 mm, OR = 1.88 (95% CI, 1.02–3.47) – AoAC >0, OR = 4.29 (95% CI, 2.30–7.97) – ABI <1.1, OR = 1.78 (95% CI, 1.16–2.74) • For most outcomes, a dose-response relationship was observed between pack-years of smoking and daily consumption for current and former smokers. Time since cessation was linearly associated with less atherosclerotic burden for all four outcomes • p for trend <0.05	—
Kianoush et al. (2017)	• Cross-sectional study (Brazilian Longitudinal Study of Adult Health) • 14,103 civil servants, 35–74 years of age; 45% men; multiethnic (52% White, 28% Brown [mixed], 16% Black, and 4% Asian or other); 30% former smokers, free of prevalent disease (including CVD) • 2008–2010 • Brazil (multicenter cohort, six cities) • Outcomes: mean carotid IMT, ABI, and CAC	• Compared with never smokers, former smokers had higher IMT and odds of ABI ≤1.0 (p = <.001) • Compared with never smokers, current smokers had higher IMT, odds of ABI ≤1.0, and odds of CAC >0 (p = <.001) • Among former smokers, time since quitting was negatively associated with carotid IMT, ABI ≤1.0, and CAC >0 (p = <.001)	—

Notes: **ABI =** ankle-brachial index; **AoAC =** aortic artery calcium; **CAC =** coronary artery calcification; **CCA =** common carotid artery; **CHD =** coronary heart disease; **CVD =** cardiovascular disease; **IMT =** intimal-media thickness; **mm =** millimeters.

[a]Natural log-transformed IMT.

was not enough evidence to conclude that reducing the number of cigarettes smoked per day reduces the risk for CVD. Among current smokers, however, a dose-response relationship has been observed between the number of cigarettes smoked per day and the incidence of CVD (USDHHS 2010; Benjamin et al. 2017). The next section briefly summarizes the evidence that supports these conclusions.

Intervention Studies

Much of the evidence linking smoking cessation to reduced risk of CVD morbidity and mortality is based on observational studies, but the link has also been observed in intervention studies directed at increasing cessation. The 1990 Surgeon General's report, which summarized results from several clinical trials, found that, overall, such interventions tend to decrease risk of CHD or CVD mortality. Among these studies, some had interventions directed at only smoking cessation, and others addressed risk factors in addition to smoking (USDHHS 1990). For some of these studies, findings from long-term follow-up have been reported subsequently.

One example is the Lung Health Study, a clinical trial started in 1986 that compared a 10-week smoking cessation program with usual care among 5,887 smokers with asymptomatic airway obstruction (Anthonisen et al. 2005). The intervention involved strong messaging by a physician and a total of twelve 2-hour group sessions using behavior modification and nicotine gum. Those who quit smoking entered a maintenance program that focused on coping skills; this group was described as the special-intervention group.

Part of the intervention group received ipratropium, a treatment for chronic obstructive pulmonary disease and asthma, and the rest of that group received a placebo inhaler. A separate group (controls) received care as usual. Over 14 years of follow-up, the all-cause mortality rate was higher in the usual-care group than in the special-intervention group (hazard ratio [HR] = 1.18; 95% CI, 1.02–1.37). The benefit of cessation was most pronounced among the 21.7% of the special-intervention group who had quit smoking at 5 years (only 5.4% of usual-care participants had quit). Although there were no significant differences in rates of CHD mortality or CVD mortality, these rates were lower in the special-intervention group than in the usual-care group. Finally, in observational analyses comparing sustained quitters, intermittent quitters, and continuing smokers in this study, smoking status was significantly related to unadjusted risk of CHD and CVD, with the highest risk among those who continued to smoke.

In the Oslo cardiovascular study, which began in 1972, 1,232 men free of CVD and diabetes—with total serum cholesterol levels of 6.9–8.9 millimoles/liter (mmol/L) (80% were smokers)—participated in a 5-year intervention study (Hjermann et al. 1981). At clinical visits every 6 months, those in the intervention group received dietary advice, and smokers in the intervention group were advised to quit. At 40-year follow-up, the intervention group had a reduced risk of death from MI versus the control group (HR = 0.71; 95% CI, 0.51–1.00). Most of the reduction in MI risk occurred during the first 15 years of follow-up; the survival curves for MI were parallel after that point (Holme et al. 2016). There was no significant difference in all-cause mortality from MI at 40 years, although there was a reduction in risk of dying among the intervention group across the first 15 years that was statistically significant at follow-up. At 5-year follow-up, the rate of CHD, MI, and SCD combined was 47% lower in the intervention group than in the control group, with an estimated 25% of the benefit attributable to smoking cessation (Hjermann et al. 1981). Follow-up at 8.5 years found a significant reduction in CHD incidence, similar to that found at 5 years, among the intervention group compared with the control group; this analysis also observed increases in the rate of smoking in the intervention group after the end of the trial (Hjermann et al. 1986).

In the Multiple Risk Factor Intervention Trial (MRFIT), which was initiated in 1973, 12,866 men at high risk of CHD were randomized to usual care or to a multifactor special intervention aimed at lowering serum cholesterol and blood pressure and promoting smoking cessation. Over follow-up averaging 7 years (during the active-intervention period), the rates of the composite outcomes of fatal or nonfatal CHD and of fatal or nonfatal CVD were significantly lower in the special-intervention group than in the usual-care group, by 14% (95% CI, 3–24%) for CHD and by 11% (95% CI, 1–21%) for CVD (Stamler et al. 2012). Rates of a priori defined endpoints (CHD death, CHD death or nonfatal MI, CVD death, and all-cause death), however, did not differ significantly between the two groups, possibly because of inadequate statistical power (Multiple Risk Factor Intervention Trial Research Group 1982; Gotto Jr 1997). Importantly, because the interventions in the MRFIT and the Oslo cardiovascular study did not focus solely on smoking cessation, the effects of the smoking cessation intervention cannot be readily separated from the effects of the other interventions.

Observational Studies

Much evidence from observational studies supports previous conclusions that smoking cessation decreases risk of CVD. Based on analyses of mortality in two historical cohorts (Cancer Prevention Study I [CPS I, 1959–1965] and II [CPS II, 1982–1988]) and five contemporary cohorts followed from 2000 to 2010, Thun and colleagues

(2013a) concluded that smoking cessation at any age reduces the risk of smoking-related death, including death from CVD; that much of the excess risk of all-cause mortality can be avoided by quitting smoking before 40 years of age, with additional benefit from quitting earlier (Doll et al. 2004; Jha et al. 2013; Pirie et al. 2013); and that quitting smoking completely is much more beneficial than reducing the number of cigarettes smoked per day. For example, an analysis of data from the National Health Interview Survey found that, on average, smokers who quit at 25–34 years of age gained 10 years of life compared with those who continued to smoke; smokers who quit at 35–44 years of age gained 9 years; and smokers who quit at 45–54 years of age gained 6 years (Jha et al. 2013). Similarly, the 50-year analysis of the British Doctors' Study showed that, among men born close to 1920, long-term cigarette smoking beginning in early adulthood tripled age-specific mortality rates, while quitting at 50 years of age halved the hazard and quitting at 30 years of age avoided most of the hazard (Doll et al. 2004).

Mons and colleagues (2015), who performed a pooled analysis of individual-level data from European and U.S. cohorts (Consortium on Health and Ageing: Network of Cohorts in Europe and the United States [CHANCES]), assessed the relationship between smoking cessation and risk of cardiovascular mortality in women and men 60 years of age and older. Smoking was strongly related to increased cardiovascular mortality; compared with current smokers, the adjusted HR of cardiovascular mortality in former smokers was lower by 0.85 for each 10 years of smoking cessation (95% CI, 0.82–0.89), providing evidence of the benefit of smoking cessation among adults 60 years of age and older. Former smokers had a higher risk of cardiovascular mortality than never smokers (Table 4.12 and Figures 4.2a and 4.2b), but the evidence suggests a trend of decreasing excess risk as the number of years since cessation increases (Table 4.12).

Mons and colleagues (2015) also measured the relationships between smoking cessation and risk advancement periods, which are the average periods of time by which the occurrence of an outcome (such as death) attributable to a risk factor is advanced in exposed versus nonexposed persons (Brenner et al. 1993; Mons et al. 2015). In general, the risk advancement period decreased as time since smoking cessation increased. For instance, risk advancement periods ranged from 3.75 years (95% CI, 2.78–4.71) among those who had quit more than 5 years earlier to -0.79 years (95% CI, -0.12–1.69) among those who had quit 20 or more years earlier.

Many studies have assessed the relationships between time since cessation or cumulative exposure and CVD risk. For example, in the Nurses' Health Study, former cigarette smokers had an increased risk of vascular mortality compared with never smokers (adjusted HR = 1.32; 95% CI, 1.20–1.44) (Kenfield et al. 2008), and compared with current smokers, the risk of vascular mortality trended downward with increased time since cessation (from <5 years to ≥20 years). In the ARIC study of Whites and African Americans, former smokers had a 17% significantly greater risk of CVD (defined as MI or stroke) compared with never smokers, with similar elevations observed by race and sex (Table 4.13) (Huxley et al. 2012). The benefit of smoking cessation increased as time since cessation increased; those who had quit 10 or more years earlier had a 33% lower risk of CVD than those who continued to smoke (Table 4.13). In the MESA cohort, former smokers (median cessation at 22 years of age [+/- 13 years]) did not have a significantly higher adjusted HR for all-cause CVD compared with never smokers (Table 4.13) (McEvoy et al. 2015a). Among current smokers in that same cohort, there was a dose-response relationship, as more pack-years were associated with a higher risk of CVD, but this trend was not observed among former smokers. Another analysis of data from the MESA cohort found that former smokers—regardless of duration, intensity, or recency of cessation—were not at increased risk of CVD compared with never smokers (Nance et al. 2017).

Similar findings have been observed in many different populations. For example, in a cohort in China, deaths attributable to tobacco-related causes trended downward with increased time since smoking cessation (He et al. 2014). A similar pattern was observed in that study for deaths attributable to vascular causes (CHD or stroke), where compared with current smokers, those who had quit for 2–7 years had 0.82 times (95% CI, 0.46–1.47) the risk and those who had quit for 8 or more years had 0.71 times (95% CI, 0.42–1.20) the risk. This pattern did not hold for all subtypes of vascular disease, but there were limited cases within these categories. In Japan, in a cohort of healthy, young, and middle-aged persons, adjusted risk of CVD events decreased as time since cessation increased, with risk being significantly lower 4 or more years after cessation (data not shown) (Kondo et al. 2011).

Similar results have been found among persons with diabetes. In a meta-analysis of persons with diabetes, former smokers had an increased risk of CVD, CVD mortality (Table 4.12), and total mortality compared with never smokers (Pan et al. 2015). In the Framingham Offspring Cohort (included in the meta-analysis by Pan and colleagues [2015]), among persons without diabetes, nonsmokers, those who had quit for 4 or fewer years, and those who had quit for more than 4 years, all had lower adjusted risks of CVD than current smokers (Table 4.13) (Clair et al. 2013). Similar patterns were observed among those with diabetes, but results were not statistically significant.

Table 4.12 Meta-analyses of observational studies on smoking cessation and incidence of total cardiovascular disease

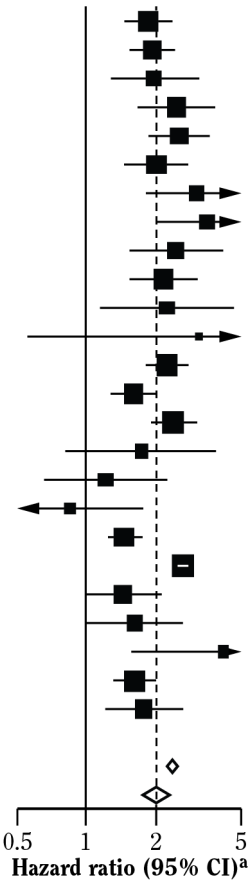
Study	Design/population	Findings: RR (95% CI)	Comments
Mons et al. (2015)[a]	• Individual-level meta-analysis • 434,278 men and women, ≥60 years of age, 47% former smokers • 31,802 CVD deaths • 25 prospective cohorts • Data collected from different cohorts in various years from the 1980s to the 2010s • Europe and North America • Mean follow-up: 1.6–14.8 years (approximately 8–13 years for most studies) • Outcome: CVD mortality	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.37 (1.25–1.49) – Current smoker: 2.07 (1.82–2.36) • Years since smoking cessation (never vs. former smoker): – Never smoker: 1.00 (referent) – Former smoker: ○ <5: 1.74 (1.51–2.01) ○ 5–9: 1.60 (1.36–1.88) ○ 10–19: 1.43 (1.24–1.64) ○ ≥20: 1.15 (1.02–1.30) • Years since smoking cessation (current vs. former smoker): – Current smoker: 1.00 (referent) – Former smoker: ○ <5: 0.90 (0.81–1.00) ○ 5–9: 0.84 (0.73–0.95) ○ 10–19: 0.78 (0.71–0.85) ○ ≥20: 0.61 (0.54–0.69)	Figure 1 in Mons and colleagues (2015) provides more details on results by smoking status
Pan et al. (2015)[a]	• Meta-analysis • Men and women, >18 years of age with type 1 or type 2 diabetes mellitus • Prospective cohort studies: – CVD: 7 studies for former smokers, 16 studies for current smokers – CVD mortality: 8 studies for former smokers, 13 studies for current smokers • Sample: – CVD: n = 1,028,982; cases = 94,929 – CVD mortality: n = 37,550; cases = 3,163 • United States, Europe, China, New Zealand, Australia, and other international collaborations • Studies included in the meta-analysis were published between 1989 and 2015 • Outcomes: CVD and CVD mortality	• CVD: – Never smoker: 1.00 (referent) – Former smoker: 1.09 (1.05–1.13) – Current smoker: 1.44 (1.34–1.54) • CVD mortality: – Never smoker: 1.00 (referent) – Former smoker: 1.15 (1.00–1.32) – Current smoker: 1.49 (1.29–1.71)	—

Notes: **CI =** confidence interval; **CVD =** cardiovascular disease; **RR =** risk ratio.

[a]Some overlap exists between the cohorts included in these publications.

Figure 4.2a Results from the meta-analyses of the association between current and never smoking status and cardiovascular mortality

Study	Number of events/total	Hazard ratio (95% CI)[a]
ELSA	777/5,128	1.94 (1.55–2.41)
EPIC-Elderly Greece	899/9,325	2.00 (1.61–2.49)
EPIC-Elderly Spain	173/5,023	2.03 (1.29–3.19)
EPIC-Elderly Sweden	148/3,165	2.56 (1.74–3.78)
EPIC-Elderly the Netherlands	277/6,561	2.63 (1.93–3.58)
ESTHER	304/5,062	2.08 (1.51–2.86)
HAPIEE Czech Republic	117/2,742	3.15 (1.90–5.23)
HAPIEE Lithuania	126/4,021	3.49 (2.10–5.81)
HAPIEE Poland	127/3,118	2.52 (1.59–3.98)
HAPIEE Russia	345/3,876	2.25 (1.59–3.17)
MORGAM Brianza	70/672	2.33 (1.19–4.55)
MORGAM Catalonia	25/725	3.20 (0.55–18.54)
MORGAM FINRISK	904/5,326	2.31 (1.88–2.83)
MORGAM Gostrup	427/2,328	1.65 (1.31–2.06)
MORGAM KORA Augsburg	712/3,060	2.50 (2.02–3.10)
MORGAM Northern Sweden	55/859	1.78 (0.83–3.83)
MORGAM SHIP Greifswald	121/1,259	1.24 (0.66–2.33)
MORGAM Warsaw	53/360	0.86 (0.41–1.82)
NHANES	1,762/5,571	1.51 (1.31–1.75)
NIH-AARP	22,683/330,305	2.75 (2.63–2.87)
SENECA	296/1,850	1.48 (1.02–2.14)
SHARE	171/25,835	1.67 (1.03–2.72)
SMC	30/3,519	4.14 (1.62–10.61)
Tromsø	947/3,834	1.68 (1.39–2.02)
Zutphen	253/754	1.83 (1.23–2.71)
Summary estimates		
Fixed effects model		2.45 (2.36–2.54)
Random effects model		2.07 (1.82–2.36)



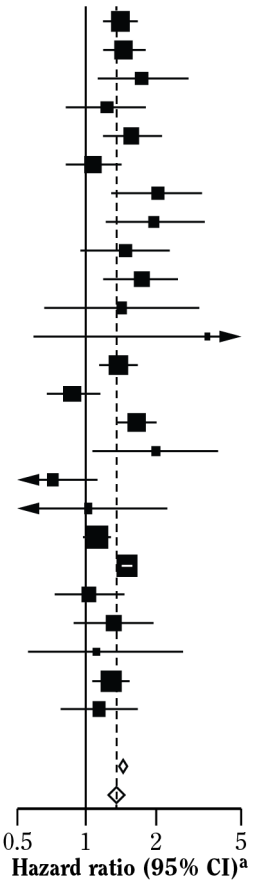
Source: Mons et al. (2015), with permission.

Note: **CI =** confidence interval; **ELSA =** English Longitudinal Study of Aging; **EPIC =** European Prospective Investigation into Cancer and Nutrition; **ESTHER =** Epidemiological Investigations on Opportunities for Prevention, Early Detection and Optimised Treatment of Chronic Diseases in the Elderly Population; **FINRISK =** a large Finnish population survey on risk factors on chronic, noncommunicable diseases; **HAPIEE =** Health, Alcohol, and Psychosocial factors In Eastern Europe; **KORA =** Kooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region); **MORGAM =** Monica Risk Genetics Archiving and Monograph; **NHANES =** National Health and Nutrition Examination Survey; **NIH-AARP =** National Institutes of Health–American Association of Retired Persons; **SENECA =** Survey Europe on Nutrition in the Elderly; **SHARE =** Survey of Health, Aging, and Retirement in Europe; **SMC =** Swedish Mammography Cohort.

[a]Test for heterogeneity: $\tau 2 = 0.023$, $p < 0.001$, $I^2 = 68.7\%$.

Figure 4.2b Results from the meta-analyses of the association between former and never smoking status and cardiovascular mortality

Study	Number of events/total	Hazard ratio (95% CI)[a]
ELSA	777/5,128	1.44 (1.22–1.69)
EPIC-Elderly Greece	899/9,325	1.50 (1.23–1.83)
EPIC-Elderly Spain	173/5,023	1.81 (1.15–2.85)
EPIC-Elderly Sweden	148/3,165	1.24 (0.83–1.87)
EPIC-Elderly the Netherlands	277/6,561	1.62 (1.22–2.16)
ESTHER	304/5,062	1.09 (0.82–1.44)
HAPIEE Czech Republic	117/2,742	2.09 (1.30–3.36)
HAPIEE Lithuania	126/4,021	2.05 (1.25–3.35)
HAPIEE Poland	127/3,118	1.51 (0.97–2.35)
HAPIEE Russia	345/3,876	1.79 (1.25–2.57)
MORGAM Brianza	70/672	1.47 (0.67–3.19)
MORGAM Catalonia	25/725	3.50 (0.59–20.78)
MORGAM FINRISK	904/5,326	1.41 (1.18–1.68)
MORGAM Gostrup	427/2,328	0.88 (0.68–1.15)
MORGAM KORA Augsburg	712/3,060	1.70 (1.41–2.06)
MORGAM Northern Sweden	55/859	2.07 (1.10–3.90)
MORGAM SHIP Greifswald	121/1,259	0.72 (0.47–1.11)
MORGAM Warsaw	53/360	1.04 (0.47–2.31)
NHANES	1,762/5,571	1.13 (1.01–1.26)
NIH-AARP	22,683/330,305	1.53 (1.48–1.58)
SENECA	296/1,850	1.04 (0.74–1.47)
SHARE	171/25,835	1.34 (0.91–1.97)
SMC	30/3,519	1.12 (0.47–2.71)
Tromsø	947/3,834	1.30 (1.09–1.55)
Zutphen	253/754	1.15 (0.78–1.69)
Summary estimates		
Fixed effects model		1.47 (1.43–1.51)
Random effects model		1.37 (1.25–1.49)



Source: Mons and colleagues (2015).

Notes: **CI =** confidence interval; **ELSA =** English Longitudinal Study of Aging; **EPIC =** European Prospective Investigation into Cancer and Nutrition; **ESTHER =** Epidemiological Investigations on Chances of Preventing, Recognizing Early and Optimally Treating Chronic Diseases in an Elderly Population; **HAPIEE =** Health, Alcohol, and Psychosocial factors In Eastern Europe; **KORA =** Kooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region); **MORGAM =** Monica Risk Genetics Archiving and Monograph; **NHANES =** National Health and Nutrition Examination Survey; **NIH-AARP =** National Institutes of Health-American Association of Retired Persons; **SENECA =** Survey Europe on Nutrition in the Elderly; **SHARE =** Survey of Health, Aging, and Retirement in Europe; **SMC =** Swedish Mammography Cohort.

[a]Test for heterogeneity: $\tau^2 = 0.067$, $P < 0.001$, $I^2 = 82.3\%$.

Table 4.13 Observational studies on smoking cessation and cardiovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Kondo et al. (2004)	• Case-control study • 29 men • Mean age: – Nonsmokers: 43.9 years of age – Smokers: 38.9 years of age • Nagoya, Japan (years not reported)	• Smoking cessation led to rapid restoration of progenitor cells and endothelial progenitor cell levels • Circulating progenitor cells and endothelial progenitor cells increased rapidly after cessation ($p < 0.0001$) and decreased after resumption of smoking to a level similar to that before cessation ($p = 0.0031$)	—
He et al. (2006)	• Cross-sectional study • 2,334 participants • 60 years of age or older • 2001–2002 • Beijing, China	• Smoking cessation was associated with decreased risks of PAD. Excess risk of PAD was nearly eliminated after stopping smoking for 10 or more years: – Never smoker (referent) – Current smoker 1.57 (1.16–2.13), $p < 0.01$ – Former smoker: 1.42 (1.02–1.98), $p < 0.05$	—
Kenfield et al. (2008)	• Prospective cohort (Nurses' Health Study) • 104,519 women • 1980–2004 • United States	• Compared with never smokers, former cigarette smokers had an increased risk of vascular mortality (adjusted HR = 1.32; 95% CI, 1.20–1.44)	Most of the excess risk of vascular mortality due to smoking can be eliminated rapidly upon cessation and within 20 years for lung diseases
Huxley et al. (2012)[a,b]	• Prospective cohort (Atherosclerosis Risk in Communities Study) • 14,200 participants with 2,777 CVD events, 45–64 years of age, 43% men, 31% former smokers at baseline, 15% quit during follow-up, African Americans (27%) and Whites, free of CHD or stroke • 1987–2007 • United States (four communities) • Mean follow-up: 17.1 years • Outcome: CVD events (myocardial infarction, stroke)	• Compared with never smokers, former smokers had a 17% higher risk of CVD • Compared with never smokers, current smokers had: – Men: 70% higher risk of CVD – Women: >200% higher risk of CVD • Years since smoking cessation (overall): – Continuous smokers: 1.00 (referent) – 1–3: 0.87 (0.67–1.14) – 4–9: 0.90 (0.69–1.16) – ≥10: 0.67 (0.45–1.01) – p trend: 0.061 (0.69 in African Americans, 0.044 in Whites)	—

Table 4.13 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Clair et al. (2013)[a,b]	• Prospective cohort (Framingham Offspring) • 3,251 participants and 631 CVD events • Baseline: mean age = 47.8 years, 48% men, mostly White, 26% quit for >4 years and 9% quit for ≤4 years, free of CVD • 1984–2011 • United States • Mean follow-up: 25 years • Outcome: CVD (defined as CHD, cerebrovascular events, PAD, or congestive heart failure)	• Among participants without diabetes mellitus: – Current smokers: 1.00 (referent) – Former smokers (quit ≤4 years): 0.47 (0.23–0.94) – Former smokers (quit >4 years): 0.46 (0.34–0.63) – Nonsmokers: 0.30 (0.21–0.44) • Similar results in those with diabetes, but not significant (included in the meta-analysis by Pan and colleagues [2015] in Table 4.13)	—
McEvoy et al. (2015a)[a]	• Prospective cohort (Multi-Ethnic Study of Atherosclerosis) • 6,814 multiethnic participants with 638 CVD events, 45–84 years of age, 47% men, 38% former smokers, free of CVD • 1996–2011 • United States • Median follow-up 10.2 years • Outcome: all-cause CVD[c]	• Risk of CVD by smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.07 (0.89–1.29) – Current smoker: 1.70 (1.32–2.18)	Median cessation among former smokers was 22 (+/-13) years; smoking exposure confirmed by levels of urinary cotinine
Nance et al. (2017)	• Multi-Ethnic Study of Atherosclerosis cohort • 6,814 participants free of clinical heart disease at baseline • 45–84 years of age • 47% men, 53% women • 2000–2002 • United States	• Former smokers—regardless of duration, intensity, or recency—were not at increased risk for suggesting that risk may drop precipitously from the time of quitting • Current smoker: – CVDH: HR = 1.98 (1.51–2.60), p <0.0005 – CVDA: HR = 1.80 (1.42–2.29), p <0.0005 – CHDH: HR = 1.94 (1.38–2.74), p <0.0005 – CHDA: HR = 1.66 (1.23–2.22), p = 0.001 • Former smoker: – CVDH: HR = 0.89 (0.72–1.11), p = 0.308 – CVDA: HR = 1.06 (0.89–1.27), p = 0.496 – CHDH: HR = 0.91 (0.69–1.20), p = 0.507 – CHDA: HR = 1.13 (0.92–1.40), p = 0.251	—

Notes: **CHD =** coronary heart disease; **CHDA =** CHDH, definite angina, probable angina if followed by revascularization; **CHDH =** coronary heart disease hard (myocardial infarction, resuscitated cardiac arrest, CHD death); **CI =** confidence interval; **CVD =** cardiovascular disease; **CVDA =** CVDH, CHDH, atherosclerotic death, CVD death; **CVDH =** CHDH, stroke death, stroke; **HR =** hazard ratio; **PAD =** peripheral artery disease; **RR =** risk ratio.

Table 4.13 Continued

[a]Measure(s) of association adjusted for covariate(s).

[b]Pooled logistic regression analyses.

[c]All-cause CVD events defined as all-cause CHD events plus cerebrovascular accident (CVA), transient ischemic attack, or ischemic or hemorrhagic stroke; CVA death; and other CVD death.

Summary of the Evidence

The additional evidence reviewed in this section strengthens the basis for previous conclusions that smoking cessation reduces the risk of CVD morbidity and mortality. For those who quit, there are short-term benefits in terms of reduced risk for CVD and a continued decline over the long term as time since cessation increases.

Smoking Cessation and Coronary Heart Disease

CHD, the most common form of heart disease in the United States, results in part from the buildup of plaque (atherosclerosis) on the walls of coronary arteries (Centers for Disease Control and Prevention [CDC] 2015). MI, or heart attack, occurs when the flow of blood to part of the heart muscle is reduced or blocked, damaging that part of the heart muscle or causing it to die. The main cause of MI is plaque in the coronary arteries; a less common cause is severe spasm or contraction of a coronary artery (CDC 2017).

In the United States, someone has an MI once every 40 seconds (Benjamin et al. 2017). Approximately 7.9 million adults (20 years of age or older) have had an MI, and 8.7 million have angina pectoris (Benjamin et al. 2017).

In the CHANCES study of women and men 60 years of age or older, cigarette smoking was strongly associated with acute coronary events (confirmed fatal and nonfatal coronary events, such as acute MI, unstable angina pectoris, or coronary death) (Mons et al. 2015). Overall, risk of acute coronary events was higher in former smokers than in never smokers, and compared with risk among current smokers, risk of acute coronary events in former smokers decreased greatly as the number of years since cessation increased (Table 4.14). Compared with current smokers, the adjusted HR of acute coronary events decreased by 0.83 for every 10 years of smoking cessation (95% CI, 0.78–0.89).

Similarly, in pooled analyses of two older cohorts and five contemporary cohorts that were restricted to men and women 55 years of age or older, smoking cessation was associated with lower rates of death from CHD compared with the rate of current smokers, but risk of CHD death was higher among former smokers compared with never smokers (Table 4.14) (Thun et al. 2013a). Among the five contemporary cohorts in that study, benefits generally increased among those who had quit at younger ages or who had quit for longer periods of time, but compared with the risk among never smokers, risks remained elevated for many years. Among women who had quit for 30 or more years and among men who had quit for 40 or more years, risk of CHD death was similar to that of never smokers. Risks of CHD mortality were not elevated among men and women who had quit before they were 40 years of age. Similar results, showing that the greatest benefit occurred among those who had quit at younger ages, were observed in a large cohort study of women in the United Kingdom (Table 4.15) (Pirie et al. 2013).

The 2014 Surgeon General's report (USDHHS 2014) noted that the pattern of declining CHD risk with increasing time since cessation was not as strong among the contemporary cohorts analyzed by Thun and colleagues (2013a) as with earlier observational analyses (including the Lung Health Study and MRFIT cohorts) that reported a larger decline in CVD risk as time since cessation increased. The report attributed this difference to the fact that analyses by Thun and colleagues (2013a) focused on older adults.

In a meta-analysis of studies comparing smoking as a risk factor for CHD in women and men, the adjusted relative risk (RR) of CHD was higher in women than in men for current cigarette smokers compared with nonsmokers, but the risk did not differ between women and men who were former smokers (Huxley and Woodward 2011).

Pujades-Rodriguez and colleagues (2015) reported on the relationship between smoking and initial presentations of CVD in the CALIBER (ClinicAl research using LInked Bespoke studies and Electronic health Records) (University College London n.d.), drawing on linked electronic health records of 1.93 million persons 30 years of age or older in England. In age-adjusted analyses (stratified by sex and general practice), the hazards of stable angina, unstable angina, MI, and sudden coronary death decreased gradually with increasing time since smoking cessation (Table 4.15). After 10 years of cessation, former smokers tended to have the same hazard of CHD outcomes as never smokers (not shown in table), although the HR for sudden coronary death in women (HR = 2.74; 95% CI, 1.36–5.51) remained elevated. The main analysis imputed smoking status for 523,611 participants. Results were similar for complete case analyses (1.41 million persons with smoking status) and when adjusting for other variables. It is unclear, however, how many persons in this study had missing covariates and whether any analyses were run without imputed covariates, which could have influenced the validity of the findings.

In the Nurses' Health Study (included in the pooled analysis by Thun and colleagues [2013]), former smokers had an increased risk of CHD mortality compared with never smokers (adjusted HR = 1.24; 95% CI, 1.09–1.42) (Kenfield et al. 2008). Compared with current smokers, former smokers showed a trend of decreased risk of CHD mortality with increased time since cessation (from fewer than 5 years to 20 or more years). In this study, former smoking was also associated with risk of all CHD events

Table 4.14 Meta-analyses and a pooled analysis of observational studies on smoking cessation and incidence of coronary heart disease

Study	Design/population	Findings: RR (95% CI)	Comments
Thun et al. (2013a)[a,b]	• Pooled analysis • Men and women, ≥55 years of age • Two historical cohorts (CPS I and II) and five contemporary cohorts:[b] – CPS I: n = 518,982; cases = 17,809 – CPS II: n = 746,485; cases = 16,308 – Contemporary cohorts: n = 956,756; cases = 22,622 • United States • Follow-up: – CPS I: 1959–1965 – CPS II: 1982–1988 – Contemporary cohorts: 2000–2010 • Outcome: CHD deaths	• CPS I: – Men: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.28 (1.21–1.36) ○ Current smoker: 1.69 (1.61–1.77) – Women: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.39 (1.22–1.59) ○ Current smoker: 1.56 (1.46–1.67) • CPS II: – Men: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.27 (1.21–1.33) ○ Current smoker: 1.78 (1.69–1.88) – Women: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.27 (1.19–1.36) ○ Current smoker: 2.00 (1.88–2.13) • Contemporary cohorts: – Men: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.43 (1.37–1.48) ○ Current smoker: 2.50 (2.34–2.66) – Women: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.44 (1.38–1.51) ○ Current smoker: 2.86 (2.65–3.08)	—

Table 4.14 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Mons et al. (2015) [a,b]	• Individual-level meta-analysis of 19 prospective cohorts • 64,221 men and women, ≥60 years of age, 47% former smokers, excluded those with a history of acute coronary events • Europe • Studies included data collected from different cohorts from various years from the 1980s to the 2010s • Mean follow-up: 1.6–14.8 years (approximately 8–13 years for most studies) • Outcome: acute coronary events	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.18 (1.06–1.32) – Current smoker: 1.98 (1.75–2.25) • Years since smoking cessation: – Current smoker: 1.00 (referent) – <5: 0.84 (0.72–0.98) – 5–9: 0.86 (0.72–1.02) – 10–19: 0.69 (0.58–0.82) – ≥20: 0.58 (0.46–0.72)	—
Pan et al. (2015) [a]	• Meta-analysis of prospective cohort studies: • 13 studies of former smokers • 21 studies of current smokers • 1,009,457 men and women, >18 years of age with diabetes mellitus (type 1 or 2), 38,752 cases • Studies in the meta-analysis were published between 1989 and 2015 • United States, Europe, China, New Zealand, and other international collaborations • Outcome: CHD	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.14 (1.00–1.30) – Current smoker: 1.51 (1.41–1.62)	—

Notes: **CHD =** coronary heart disease; **CI =** confidence interval; **CPS =** Cancer Prevention Study; **RR =** risk ratio.

[a]There was some overlap between cohorts included in two or more of these publications in this table.

[b]Historical cohorts: CPS I (1959–1965) and CPS II (1982–1988). Contemporary cohorts (2000–2010): National Institutes of Health–American Association of Retired Persons Diet and Health Study, CPS II Nutrition Cohort, Women's Health Initiative (women only), Nurses' Health Study (women only), and Health Professionals Follow-Up Study (men only).

Table 4.15 Observational studies on smoking cessation and incident coronary heart disease

Study	Design/population	Findings: RR (95% CI)	Comments
Song and Cho (2008)[a]	• Prospective cohort • 475,734 men, 30–58 years of age in 1990, 6% quitters,[b] 16% ex-smokers,[b] free of stroke or myocardial infarction, 2,164 cases of CHD • 1992–2001 • Korea • Mean follow-up: 8.83 years • Outcome: myocardial infarction • Nonreducing heavy smoker (>20 cigarettes per day), moderate smoker (10–19 cigarettes per day), light smoker (<10 cigarettes per day); reducer from heavy to moderate smoking; reducer from heavy to light smoking; reducer from moderate to light smoking; quitter from any smoking status; sustained ex-smoker; and sustained never smoker	• Smoking status:b – Current smoker (by smoking intensity): ○ Non-reducing heavy smoker 1.00 (referent) ○ Moderate smoker: 0.74 (0.65–0.85) ○ Light smoker: 0.65 (0.57–0.75) – Quitter: 0.43 (0.34–0.53) – Sustained ex-smoker: 0.37 (0.32–0.44) – Never smoker: 0.29 (0.25–0.34)	Women not included because of their low percentage of smoking
Pirie et al. (2013)[a]	• Prospective cohort (Million Women Study) • 1.2 million women; 55 years of age (median) at baseline; 28% former smokers; free of prior cancer (other than nonmelanoma skin cancer), heart disease, stroke, and current respiratory disease treatment; 4,458 cases of CHD among never or current smokers • 1996–2011 • United Kingdom • Mean follow-up: 12 years • Outcome: CHD mortality	• Age (in years) quit smoking: – Never smoker: 1.00 (referent) – <25: 0.8 – 25–34: 1.0 – 35–44: 1.4[c] – 45–54: 1.9	Exact CIs not reported for these results; total number of CHD cases not provided
McEvoy et al. (2015a)[a]	• Prospective cohort (Multi-Ethnic Study of Atherosclerosis) • 6,814 participants, 45–84 years of age, 47% men, multiethnic, 38% former smokers, free of CVD at baseline; 284 hard CHD events and 449 all-cause CHD events • 1996–2011 • United States • Median follow-up: 10.2 years • Outcomes: hard CHD and all-cause CHD[d]	• Hard CHD events: – Never smoker: 1.00 (referent) – Former smoker: 0.93 (0.70–1.24) – Current smoker: 1.70 (1.18–2.45) • All-cause CHD events: – Never smoker: 1.00 (referent) – Former smoker: 1.14 (0.91–1.42) – Current smoker: 1.55 (1.14–2.10)	Median length of cessation among former smokers was 22 (+/-13) years; smoking exposure confirmed by urinary cotinine

Table 4.15 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Pujades-Rodriguez et al. (2015)	Prospective cohort • 1.93 million participants, ≥30 years of age, 49% men, predominantly White (also South Asian and Black), 16.2% former smokers (among those with smoking data); drawn from CALIBER program (linked electronic health records); no history of CVD, 4,253 cases of myocardial infarction in former smokers • 1997–2010 • England • Median follow-up: 6 years	• Myocardial infarction by smoking status (age-adjusted): – Current smoker: 1.00 (referent) – Former smoker (years since quitting): ○ <2: 0.55 (0.34–0.88) ○ 2–9: 0.52 (0.41–0.65) ○ ≥10: 0.45 (0.38–0.55) • Stronger association with more time since cessation for outcomes of unheralded coronary death and unstable angina – Former smoker (years since quitting): ○ <2: 1.01 (0.60–1.71) ○ 2–9: 0.76 (0.47–1.23) ○ ≥10: 0.61 (0.41–0.89) – Former smoker (years since quitting): ○ <2: 1.05 (0.55–1.99) ○ 2–9: 0.86 (0.63–1.18) ○ ≥10: 0.63 (0.52–0.77) • Weaker trend for outcome of stable angina – Former smoker (years since quitting): ○ <2: 1.03 (0.66–1.60) ○ 2–9: 0.88 (0.69–1.12) ○ ≥10: 0.81 (0.81–0.99)	Imputed smoking status in the main analyses, as smoking data were missing in 523,611 participants; results were similar for complete case analysis (1.41 million participants with smoking status) and when adjusted for other potential confounders; unclear how many persons had missing covariates and whether analyses were run without imputed covariates, which might have influenced validity of findings

Notes: **CALIBER =** Clinical research using LInked Bespoke studies and Electronic health Records; **CHD =** coronary heart disease; **CI =** confidence interval; **CVD =** cardiovascular disease; **RR =** risk ratio.

[a]Measure(s) of association adjusted for covariate(s).

[b]Smoking categories based on smoking status in 1990 baseline exam and change in status from 1990 to 1992 exams: non-reducing heavy smoker (≥20 cigarettes per day), moderate smoker (10–19 cigarettes per day), light smoker (<10 cigarettes per day), reducer from heavy to moderate, reducer from heavy to light, reducer from moderate to light, quitter from any smoking status, sustained ex-smoker, sustained never smoker. Results for reducers not shown in table.

[c]Lower boundary of 95% CI >1.0.

[d]Hard CHD events defined as myocardial infarction or death from CHD. All-cause CHD events defined as hard CHD events plus definite angina, probable angina resulting in revascularization, and resuscitation after cardiac arrest.

(fatal and nonfatal), but there was a stronger association for current smokers than for former smokers (Hu et al. 2000; Stampfer et al. 2000). In the MESA cohort, former smokers (median cessation: 22 years [+/- 13 years]) did not have a higher adjusted hazard for either a more strictly defined or a more broadly defined CHD outcome (Table 4.15) (McEvoy et al. 2015a). Despite a positive dose-response relationship between pack-years of smoking and CHD among current smokers, the dose-response relationship was null among former smokers (data not shown). Both a high-sensitivity CRP ≥3 mg/L and, particularly, a CAC >100 identified current smokers with a higher RR of CHD. In a large cohort of Korean men, both those who quit smoking within 2 years before the start of follow-up and those who had quit for a longer period had a lower adjusted hazard of MI compared with current heavy smokers (Table 4.15) (Song and Cho 2008).

Lee and colleagues (2012) used a negative exponential distribution to quantitatively estimate how rapidly the risk of CHD declines following smoking cessation. Estimates from this approach were used to inform a special report from the American Heart Association and the American College of Cardiology on the longitudinal risks and benefits of therapies to prevent cardiovascular problems among Medicare patients (Lloyd-Jones et al. 2017). Based on a literature search and on consultation within their own team and with biostatistical and content experts, Lloyd-Jones and colleagues (2017) concluded that the approach set forth by Lee and colleagues (2012) was the most rigorous methodology for estimating the longitudinal reduction in MI risk associated with tobacco cessation. The quantitative review by Lee and colleagues (2012) had estimated that the excess risk of CHD associated with smoking decreased by 50% at 4.40 years after cessation (95% CI, 3.26–5.95), but there was a substantial range in the estimate of the time required to achieve a 50% decrease in CHD risk across the studies, from less than 2 years to greater than 10 years. The cohort studies considered by Lee and colleagues (2012) had little follow-up time after 2000, and alternative models to the negative exponential model were not considered. It should be noted that Philip Morris funded the research for this paper.

In line with IARC (2007), the risk of MI appears to decrease asymptotically as time since cessation increases, eventually reaching the risk among never smokers. In another modeling paper, Hurley (2005) also observed a rapid decrease in the risk of acute MI within 1–2 years of cessation, followed by a slower decline thereafter.

Summary of the Evidence

Building on evidence reviewed in previous Surgeon General's reports, additional studies have added to the evidence base indicating that smoking cessation reduces the risk of CHD. The risk declines rapidly in the period immediately following cessation and then declines at a slower rate in the longer term. In some studies, the risk for CHD in former smokers eventually decreases to that of never smokers.

Smoking Cessation and Cerebrovascular Disease

Cerebrovascular disease results from interruptions in the flow of arterial blood to the brain, resulting in a syndrome of mild-to-severe neurologic deficits. Deficits can be temporary (transient ischemic attack) or permanent (stroke). In the United States, cerebrovascular disease is the fifth leading cause of death (Kochanek et al. 2016), responsible for approximately 140,000 deaths each year (Yang et al. 2017). In 2017 it was estimated that 7.7 million U.S. adults 18 years of age or older have had a stroke (Benjamin et al. 2017). Ischemic stroke, which results from an obstruction in a blood vessel that blocks the supply of blood to the brain, accounts for an estimated 87% of strokes in the United States (Benjamin et al. 2017). Hemorrhagic stroke occurs when a weakened blood vessel ruptures and causes either an intracerebral (within the brain) hemorrhage (ICH) or a subarachnoid hemorrhage (SAH). From 2014 to 2015, the annual direct (medical) plus indirect costs of stroke in the United States was estimated to be $45.5 billion (Benjamin et al. 2019). Heidenreich and colleagues (2011) projected that the direct (medical) cost of stroke will increase by 238% from 2010 to 2030.

Previous Surgeon General's reports (USDHHS 1989, 2004) have concluded that smoking is a cause of stroke. The 1990 Surgeon General's report concluded that smoking cessation reduces the risk of both ischemic stroke and SAH compared with continued smoking, and that the risk of stroke returns to that of never smokers 5–15 years after quitting (USDHHS 1990) (Table 4.10). Similarly, the 2001 Surgeon General's report concluded that in most studies including women, the increased risk for stroke associated with smoking is reversible after smoking cessation; after 5–15 years of abstinence, the risk among former smokers approaches that of women who have never smoked (USDHHS 2001) (Table 4.10).

Several pooled studies or meta-analyses have found that smoking cessation is associated with a reduced risk of stroke or stroke mortality (Table 4.16) (Feigin et al. 2005; Peters et al. 2013; Thun et al. 2013a; Mons et al. 2015; Pan et al. 2015). Peters and colleagues (2013), in a meta-analysis of prospective cohort studies from around the world that were published between January 1, 1966, and

Table 4.16 Observational studies (meta-analyses and pooled analyses) on smoking cessation and cerebrovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Feigin et al. (2005)[a]	• Meta-analysis of five longitudinal studies and three case-control studies • Men and women • Number of cases for analysis of current smoking: – Longitudinal studies: 453 – Case-control studies: 607 • Follow-up: 5–22 years • Studies included in the meta-analysis were published between 1966 and 2015 • United States, Europe, and Asia-Pacific region • Outcome: subarachnoid hemorrhage	• Longitudinal studies: – Never smoker vs. former smoker: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.9 (1.5–2.3) – Nonsmoker vs. current smoker: ○ Nonsmoker: 1.00 (referent) ○ Current smoker: 2.2 (1.3–3.6) • Case-control studies: – Never smoker vs. former smoker: ○ Never smoker: 1.00 (referent) ○ Former smoker: 2.3 (2.2–2.4) – Nonsmoker vs. former smoker: ○ Nonsmoker: 1.00 (referent) ○ Current smoker: 3.1 (2.7–3.5)	—

Table 4.16 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Thun et al. (2013a)[a,b]	• Pooled analysis • Men and women, ≥55 years of age • Two historical cohorts (CPS I and II) and five contemporary cohorts[c] • Sample: – CPS I: n = 518,982; 5,890 deaths from stroke – CPS II: n = 746,485; 4,037 deaths from stroke • Contemporary cohorts: 956,756; 7,536 • United States • Follow-up: – CPS I: 1959–1965 – CPS II: 1982–1988 • Contemporary cohorts: 2000–2010 • Outcome: deaths from stroke	• CPS I: – Men: ○ Never smoker: 1.00 (referent) ○ Former smoker: 0.95 (0.83–1.09) ○ Current smoker: 1.38 (1.26–1.52) – Women: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.46 (1.19–1.78) ○ Current smoker: 1.51 (1.35–1.69) • CPS II: – Men: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.07 (0.95–1.20) ○ Current smoker: 1.97 (1.74–2.23) – Women: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.16 (1.03–1.31) ○ Current smoker: 2.19 (1.96–2.44) • Contemporary cohorts: – Men: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.16 (1.07–1.25) ○ Current smoker: 1.92 (1.66–2.21) – Women: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.15 (1.07–1.22) ○ Current smoker: 2.10 (1.87–2.36)	—
Peters et al. (2013)[a]	• Meta-analysis of prospective cohorts – Current smokers: 76 cohorts – Former smokers: 72 cohorts • Men and women, ≥18 years of age: – Current smokers: n = 3,817,289; 39,042 cases of stroke – Former smokers: n = 3,534,330; 36,449 cases of stroke • Studies in the meta-analysis were published between January 1, 1996, and January 26, 2013 • United States, Europe, and Asia-Pacific region • Outcome: fatal and nonfatal stroke	• Men: – Never smoker: 1.00 (referent) – Former smoker: 1.08 (1.03–1.13) – Nonsmoker: 1.00 (referent) – Current smoker: 1.67 (1.49–1.88) • Women: – Never smoker: 1.00 (referent) – Former smoker: 1.17 (1.12–1.22) – Nonsmoker: 1.00 (referent) – Current smoker: 1.83 (1.58–2.12)	—

Table 4.16 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Mons et al. (2015)[a,b]	• Individual-level meta-analysis of 19 prospective cohorts • 66,136 men and women, ≥60 years of age, approximately 47% former smokers, excluded those with a history of stroke, 4,052 cases of stroke • Years of data collection: not provided • Europe • Mean follow-up: 1.6–14.8 years (8–13 years • for most studies) • Outcome: stroke	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.17 (1.07–1.26) – Current smoker: 1.58 (1.40–1.78) • Years since quitting: – Current smoker: 1.00 (referent) – Former smoker: ○ <5: 0.97 (0.79–1.19) ○ 5–9: 0.98 (0.74–1.31) ○ 10–19: 0.79 (0.69–0.92) ○ ≥20: 0.67 (0.60–0.76)	—
Pan et al. (2015)	• Meta-analysis of prospective cohort studies: – 9 studies of former smokers – 15 studies of current smokers • 1,013,724 men and women >18 years of age with diabetes mellitus (type 1 or 2); 33,170 cases of stroke • Studies in the meta-analysis were published between 1989 and 2015 • United States, Europe, China, and other international collaborations • Outcome: stroke	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.04 (0.87–1.23) – Current smoker: 1.54 (1.41–1.69)	—

Notes: **CI =** confidence interval; **CPS =** Cancer Prevention Study; **RR =** risk ratio.

[a]There was some overlap between cohorts that were included in two or more of the publications in this table.

[b]Historical cohorts: CPS I (1959–1965) and CPS II (1982–1988).

[c]Contemporary cohorts (2000–2010): National Institutes of Health–American Association of Retired Persons Diet and Health Study, CPS II Nutrition Cohort, Women's Health Initiative (women only), Nurses' Health Study (women only), and Health Professionals Follow-Up Study (men only).

January 26, 2013, found that, compared with nonsmokers (who were either never smokers or former smokers), the risk of stroke in current smokers was 83% higher (95% CI, 1.58–2.12) for women and 67% higher for men (95% CI, 1.49–1.88) (Table 4.16) (Peters et al. 2013). Compared with never smoking, former smoking was associated with a 17% higher risk of stroke among women (95% CI, 1.12–1.22) and an 8% higher risk among men (95% CI, 1.03–1.13). There was no evidence of a difference in the benefit of smoking cessation between women and men. This analysis did not evaluate the relationships between risk of stroke and smoking duration or time since quitting.

Mons and colleagues (2015) examined individual data from the CHANCES study (European and North American cohorts) to assess the relationship between smoking cessation and risk of stroke in women and men 60 years of age or older, and found that smoking was strongly associated with increased risk of stroke. Overall, former smokers had a higher risk of stroke than never smokers. Compared with current smokers, there was a dose-response relationship, with risk decreasing among former smokers as years since cessation increased (Table 4.16). In this comparison, the adjusted HR of stroke was 0.87 for every 10 years of smoking cessation (95% CI, 0.84–0.91). Similarly, Thun and colleagues (2013a) reported that smoking cessation reduced rates of death from stroke in two older and five contemporary cohorts restricted to men and women 55 years of age or older (Table 4.16), with a greater benefit generally found among those who had quit at younger ages. Risk of stroke mortality among former smokers tended to decrease as time since cessation increased.

Similarly, in a large cohort study of women in the United Kingdom, most of the benefit from cessation occurred among those who had quit at younger ages (Table 4.17) (Pirie et al. 2013). Elsewhere, in the Nurses' Health Study (included in the pooled analysis by Thun and colleagues [2013]), former smokers had an increased risk of cerebrovascular mortality compared with never smokers (adjusted HR = 1.27; 95% CI, 1.06–1.51) (Kenfield et al. 2008). Compared with current smokers, risk of cerebrovascular-disease mortality decreased among former smokers with increased time since cessation (from fewer than 5 years to 20 or more years). In contrast to the Nurses' Health Study, the British Regional Heart Study found that former light smokers (1–19 cigarettes per day) did not have an increased risk of stroke when compared with never smokers; current heavy smokers (≥21 cigarettes per day), however, had an increased risk (Wannamethee et al. 1995). In that study, compared with never smokers, former smokers had 1.7 times the adjusted hazard of stroke (95% CI, 0.9–4.8); there was not a consistent pattern of decreasing risk with increased time since cessation, but this pattern was seen in some categories.

Similar findings have been reported by many other studies (Table 4.17). In a case-control study of young women (15–40 years of age) with ischemic stroke, former smokers did not have an increased risk of stroke compared with never smokers, but this study had the potential limitation of recall bias (Bhat et al. 2008). The Strong Heart Study, a population-based cohort recruited from 13 American Indian tribes/communities, found that current and former smokers had an increased adjusted hazard of stroke compared with never smokers (Zhang et al. 2008). For this study, former smoking was defined as having smoked 100 or more cigarettes in one's lifetime, having smoked cigarettes regularly in the past, and not smoking currently. In a meta-analysis of persons with diabetes mellitus, former smokers did not have an increased risk of stroke compared with never smokers (Pan et al. 2015).

In an analysis similar to the one of CHD, Lee and colleagues (2014) quantitatively estimated reduction in stroke risk following smoking cessation. In a fixed-effects model, they estimated that the excess risk of stroke associated with smoking decreased by 50% after 4.78 years of smoking abstinence (95% CI, 2.17–10.50), which is similar to the time needed to realize a 50% reduction in risk that they had estimated for CHD. There was considerable unexplained heterogeneity in the results, however, making a definitive conclusion challenging; the random-effects estimate for a 50% reduction was 3.08 years (95% CI, 1.32–7.16). Hurley (2005), in another modeling paper, observed a rapid decrease in risk of stroke shortly after cessation (within 1–2 years), followed by a slower decline.

Stroke Subtypes

Several studies have assessed relationships between smoking cessation and subtypes of stroke (SAH, ICH, and ischemic stroke) (Kawachi et al. 1993; Kurth et al. 2003a,b; Feigin et al. 2005; Sturgeon et al. 2007; Song and Cho 2008; Pujades-Rodriguez et al. 2015; Lindbohm et al. 2016).

In a meta-analysis of longitudinal and case-control studies by Feigin and colleagues (2005), former smoking was associated with twice the risk of SAH compared with never smoking (Table 4.16). Some of the studies in this meta-analysis assessed amount smoked or time since cessation or examined subtypes of stroke. Kurth and colleagues (2003a,b) assessed associations between smoking and hemorrhagic stroke subtypes in men (Physician's Health Study) and women (Women's Health Study) (Table 4.17). In both studies, former smokers and never smokers had no significant difference in risk of total hemorrhagic stroke, ICH, and SAH (Table 4.17). Earlier, Kawachi and colleagues (1993) reported that, in women in the Nurses' Health Study, the excess risk for total strokes decreased within approximately 2–4 years after smoking cessation compared with the risk among current smokers. Those

Table 4.17 Observational studies on smoking cessation and cerebrovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Kurth (2003a)[a]	• Prospective cohort (observational analyses of Women's Health Study, a randomized controlled trial) • 39,783 women, 40–84 years of age at entry, 95% White, apparently healthy and free of stroke at baseline, seven hemorrhagic strokes • 1993–2003 • United States • Mean follow-up: 9 years • Outcome: hemorrhagic stroke (and subtypes)	• Total hemorrhagic stroke: – Never smoker: 1.00 (referent) – Former smoker: 0.97 (0.55–1.72) – Current smoker (<20 cigarettes smoked per day): 1.93 (0.75–5.02) – Current smoker (≥20 cigarettes smoked per day): 3.29 (1.72–6.29) • Similar patterns for subtype analysis of intracerebral hemorrhage and subarachnoid hemorrhage	—
Kurth (2003b)[a]	• Prospective cohort (observational analyses of Physicians' Health Study, a randomized controlled trial) • 22,022 male physicians, 40–84 years of age at entry, 92% White, apparently healthy and free of stroke at baseline, 139 cases of stroke • 1982–2002 • United States • Mean follow-up: 17.8 years • Outcome: hemorrhagic stroke (and subtypes)	• Total hemorrhagic stroke: – Never smoker: 1.00 (referent) – Former smoker: 0.76 (0.53–1.09) – Current smoker (<20 cigarettes smoked per day): 1.65 (0.61–4.50) – Current smoker (≥20 cigarettes smoked per day): 2.36 (1.38–4.02) • Similar patterns for subtype analysis of intracerebral hemorrhage and subarachnoid hemorrhage	—
Bhat et al. (2008)[a]	• Case-control (Stroke Prevention in Young Women Study) • Females, 15–40 years of age, 466 cases of stroke and 604 controls (random-digit dialing; matched by age and geographic region of residence) • Recruited in 1992–1996 and 2001–2003 • United States (greater Baltimore–Washington, D.C., area) • Outcome: ischemic stroke	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.0 (0.6–1.4) – Current smoker (cigarettes smoked per day): ○ All: 2.6 (1.9–3.6) ○ 1–10: 2.2 (1.5–3.3) ○ 11–20: 2.5 (1.6–3.8) ○ 21–39: 4.3 (1.8–10) ○ ≥40: 9.1 (3.2–26)	Potential for recall bias

Table 4.17 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Song and Cho (2008)[a]	• Prospective cohort • 475,734 men, 30–58 years of age in 1990, 6% quitters,b 16% ex-smokers,b free of stroke or myocardial infarction, 6,092 cases of stroke • 1992–2001 • Korea • Mean follow-up: 8.83 years • Outcome: total stroke	• Smoking status:[b] – Current smoker: ○ Non-reducing heavy smoker ○ (≥20 cigarettes per day): 1.00 (referent) ○ Moderate smoker: (10–19 cigarettes ○ per day): 0.86 (0.78–0.93) ○ Light smoker (<10 cigarettes per day): ○ 0.84 (0.77–0.93) – Quitter: 0.70 (0.62–0.80) – Ex-smoker: 0.53 (0.48–0.58) – Never smoker: 0.57 (0.52–0.63) • Similar patterns observed for stroke subtypes (ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage): – Hemorrhagic stroke: lighter smokers and quitters did not have a significantly different risk vs. heavy smokers – Subarachnoid hemorrhage: moderate smokers (10–19 cigarettes per day) did not have a lower risk than heavy smokers (≥20 cigarettes per day)	—
Zhang et al. (2008)[a]	• Prospective cohort (Strong Heart Study) • 4,507 participants from 13 American Indian tribes/communities, 45–74 years of age, 41% men, no history of stroke, 306 events of stroke • 1989–2004 • Arizona, North Dakota, Oklahoma, and South Dakota • Mean follow-up: 13.4 years • Outcome: stroke	• Smoking status:[c] – Never smoker: 1.00 (referent) – Former smoker: 1.6 (1.14–2.25) – Current smoker: 2.38 (1.69–3.36)	—

Table 4.17 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Kim et al. (2012a)[a]	• Case-control study (multicenter) • Participants, 30–84 years of age (mean age: 50.7 years); 39% men; 426 cases and 426 age–sex-matched controls (recruited from siblings, friends, or neighbors of controls); free of stroke, dementia, or other neurological diseases • Recruited in 2002–2004 • Korea • Outcome: subarachnoid hemorrhage	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 1.79 (0.86–3.75) – Current smoker: 2.84 (1.63–4.97) • Years since quitting (current vs. former smoker): – Current smoker: 1.00 (referent) – Former smoker ○ <5: 0.94 (0.41–2.16) ○ ≥5: 0.41 (0.17–0.97) • Years since quitting (never vs. former smoker): – Never smoker: 1.00 (referent) – Former smoker: ○ <5: 2.71 (1.07–6.81) ○ ≥5: 1.17 (0.46–3.00) • Smoking intensity (current vs. former smoker): – Current smoker: 1.00 (referent) – Former smoker: ○ 1–19 cigarettes per day: 0.36 (0.13–1.01) ○ ≥20 cigarettes per day: 0.84 (0.40–1.78) • Smoking intensity (never vs. former smoker): – Never smoker: 1.00 (referent) – Former smoker: ○ 1–19 cigarettes per day: 0.99 (0.32–3.06) ○ ≥20 cigarettes per day: 2.34 (1.02–5.36)	Potential for bias because of recall and selection of controls from siblings, friends, or neighbors

Table 4.17 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Tse et al. (2012)[a]	• Prospective cohort (extension of 7-5 China Stroke Prevention Project) • 26,607 participants ≥35 years of age, 47% men, free of stroke; former smokers included 7.2% of men and 1.5% of women; 1,108 cases of stroke • 1986–2000 • China • Mean follow-up: 9.5 years • Outcomes: total stroke, ischemic stroke, and hemorrhagic stroke	• Men – Total stroke: ○ Never smoker: 1.00 (referent) ○ Former smoker: 1.35 (1.00–1.81) ○ Current smoker: 1.39 (1.15–1.67) – Similar patterns for ischemic and hemorrhagic stroke • Women: – Total stroke: ○ Never smoker: 1.00 (referent) ○ Former smoker: 0.86 (0.45–1.65) ○ Current smoker: 1.34 (1.06–1.69) – Similar patterns for ischemic and hemorrhagic stroke	Limited power to detect associations because of few former smokers
Pirie et al. (2013)[a]	• Prospective cohort (Million Women's Study) • 1.2 million women; stopped smoking before 55 years of age (at baseline); 28% former smokers, and free of prior cancer (other than nonmelanoma skin cancer), heart disease, stroke, and current respiratory disease treatment; 2,986 cases of cerebrovascular disease among never or current smokers • 1996–2011 • United Kingdom • Mean follow-up: 12 years • Outcome: cerebrovascular disease mortality	• Age (in years) quit smoking – Never smoker: 1.00 (referent) – <25: 0.9 – 25–34: 0.9 – 35–44: 1.1 – 45–54: 1.3[d]	Exact CIs not reported for these results; total cases of cerebrovascular disease not provided
Pujades-Rodriguez et al. (2015)	• Prospective cohort • 1.93 million participants; ≥30 years of age; 49% men, predominantly White (also South Asian and Black), and 16.2% former smokers (among those with smoking data); drawn from CALIBER program (linked electronic health records); no history of CVD; and 1,558 cases of ischemic stroke in former smokers • 1997–2010 • England • Median follow-up: 6 years	• Ischemic stroke by smoking status (age-adjusted): – Current smoker: 1.00 (referent) – Former smoker (<2 years): 0.62 (0.32–1.22) – Former smoker (2–9 years): 0.63 (0.45–0.87) – Former smoker (≥10 years): 0.51 (0.43–0.61) • Reduced risk for longer time since cessation for outcomes of transient ischemic attack, subarachnoid hemorrhage, and intracerebral hemorrhag	See Table 4.17 for concerns about validity

Table 4.17 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Lindbohm et al. (2016)[a]	• Prospective cohort (FINRISK Survey) • 65,521 participants, 45 years of age (median), 48% men, no prior subarachnoid hemorrhage at baseline, 492 cases of subarachnoid hemorrhage • 1972–2011 • Finland • Median follow-up: 21.1 years (full cohort) and 14.8 years (cases) • Outcome: subarachnoid hemorrhage	• Age quit smoking: – Never smoker: 1.00 (referent) – Recent quitter (<6 months): 1.93 (0.98–3.79) – Former smoker (quit for >6 months): 1.34 (0.98–1.82) – Current smoker (cigarettes per day): ○ 1–10: 2.54 (1.90–3.40) ○ 11–20: 2.82 (2.14–3.70) ○ 21–30: 3.79 (2.51–5.71) ○ ≥31: 3.91 (1.97–7.75)	—

Notes: **CALIBER =** Clinical research using LInked Bespoke studies and Electronic health Records; **CI =** confidence interval; **FINRISK =** a large Finnish population survey on risk factors on chronic, noncommunicable diseases; **RR =** risk ratio.

[a]Measure(s) of association adjusted for covariate(s).

[b]Smoking categories based on smoking status in 1990 exam and change from 1990 to 1992: non-reducing heavy smoker (≥20 cigarettes per day), moderate smoker (10–19 cigarettes per day), light smoker (<10 cigarettes per day), quitter from any smoking status, sustained ex-smoker, sustained never smoker. Results in reducers not shown in table.

[c]Former smoking defined as having smoked ≥100 cigarettes, having smoked cigarettes regularly in the past, and not smoking currently.

[d]Lower boundary of 95% CI >1.0 (CIs not provided).

researchers found a similar pattern of decreasing risk as time since cessation increased for ischemic stroke and SAH (Kawachi et al. 1993). Elsewhere, in a case-control study, the adjusted odds of SAH due to ruptured intracranial aneurysm were higher among current cigarette smokers than former smokers (Kissela et al. 2002).

More recent research has produced similar findings, but associations have been less consistent for ICH than for SAH (Table 4.17). In the FINRISK study cohort (a large Finnish population survey on risk factors for chronic, noncommunicable diseases) (Lindbohm et al. 2016), former smokers had a decreased risk of SAH compared with current smokers. In a nationwide, multicenter, case-control study in Korea (Kim et al. 2012a), former smokers who had quit for 5 or more years had a lower adjusted risk of SAH than current smokers. This study also found a pattern of lower risk for former smokers with lower levels of prior smoking intensity. The study, however, may have been biased because of faulty recall of smoking history and selection of controls who were siblings, friends, or neighbors. Earlier, in a large cohort of Korean men, in a comparison with heavy smokers, former smokers who quit smoking 2 years or less before the start of follow-up had a lower adjusted hazard of total stroke, ischemic stroke, and SAH (Song and Cho 2008). A similar pattern, although not statistically significant, was observed for hemorrhagic stroke. Compared with heavy smokers, former smokers who had stopped smoking for a longer period of time had lower adjusted hazards of all types of strokes. Elsewhere, in a pooled analysis of the ARIC study and the Cardiovascular Health Study, there was no clear relationship between smoking status and ICH (not shown in tables) (Sturgeon et al. 2007).

In a hospital-based case-control study comparing patients with ruptured aneurysms against controls with unruptured aneurysms, the adjusted odds of ruptured cerebral aneurysm were 1.26 (95% CI, 0.98–1.61) in current smokers versus former smokers (Can et al. 2017). In that study, former smokers had higher adjusted odds of ruptured aneurysm than never smokers (OR = 1.56; 95% CI, 1.31–1.86). These findings are in line with those in the meta-analysis performed by Feigin and colleagues (2005) that compared SAH cases with healthy controls. In this analysis, current smokers had a two- to three-fold increase in risk of SAH compared with never smokers, and the risk was approximately twice as great in former smokers as it was in never smokers.

In the electronic health records-based CALIBER program (Table 4.17), the age-adjusted hazards of transient ischemic attack, ischemic stroke, SAH, and ICH gradually decreased with increased time since smoking cessation (Pujades-Rodriguez et al. 2015). After 10 years of cessation, former smokers tended to have the same hazard of these cerebrovascular-disease outcomes as never smokers (not shown in table). Note that the section on CHD in this chapter discussed concerns about the validity of this study.

In a multicenter, population-based prospective cohort study in China (Table 4.17), men who were former smokers had a higher risk of stroke than those who were never smokers (HR = 1.35; 95% CI, 1.00–1.81) (Tse et al. 2012). Among women, there was no significant difference in this comparison (HR = 0.86; 95% CI, 0.45–1.65), but there were only 11 cases of stroke. Further, power was limited because of the low prevalence of former smokers.

Prognosis of Cerebrovascular Disease

Among four randomized controlled trials that assessed the rate of smoking cessation following cerebrovascular disease with follow-ups ranging from 6 months to 3.5 years, the overall cessation rate was 23.9% (42 of 176) among those who received a smoking cessation intervention and 20.8% (37 of 178) for those who did not receive one (Edjoc et al. 2012). Elsewhere, in a single study of 110 patients with acute stroke, 40% had stopped smoking 1 year after hospital admission; the best predictors of cessation were insular damage and a prestroke intention to stop (Suner-Soler et al. 2012). Finally, in a study of 198 patients, 21.7% gave up smoking within 6 months after their first stroke (Bak et al. 2002).

Among persons with cerebrovascular disease, findings from several studies suggest that former cigarette smokers have a lower risk of morbidity or mortality compared with those who continue to smoke after developing cerebrovascular disease. For example, in a literature review, Straus and colleagues (2002) estimated that smoking cessation would reduce the risk of a new stroke by 33% (95% CI, 29–38%) in survivors of stroke.

In a British study that followed 308 men and women with a history of stroke for an average of 7.5 years, current smokers had 2.27 times the adjusted risk of mortality (95% CI, 1.12–4.57) of never smokers, and former smokers had 1.46 times the risk (95% CI, 0.87–2.43) (Myint et al. 2006). In an Australian cohort of 1,589 cases of first-ever and recurrent stroke, among those who survived 28 days after the index event, the adjusted hazard of death or a nonfatal vascular event was higher for current smokers than former smokers (HR = 1.23; 95% CI, 1.00–1.50) (Kim et al. 2012b). In addition, former smokers had a higher adjusted hazard for such an outcome than never smokers (HR = 1.18; 95% CI, 1.01–1.39). Using data from the Registry of the Canadian Stroke Network, Edjoc and colleagues (2013) reported that, among patients with stroke, former smoking was associated with a reduced risk of the presenting stroke's severity, of mortality at 30 days, and of a prolonged stay in the hospital when compared with current smoking; the results varied by stroke subtype.

Summary of the Evidence

Building on evidence reviewed in previous Surgeon General's reports, the additional studies reviewed in this report further strengthen the evidence that smoking cessation reduces the risk of stroke morbidity and mortality and that the risk of such outcomes decreases with increased time since cessation.

Smoking Cessation and Atrial Fibrillation

Atrial fibrillation (AF) is a condition in which the atria (upper chambers of the heart) beat irregularly. Earlier estimates of the prevalence of AF in the United States ranged from approximately 2.7 to 6.1 million persons (Go et al. 2001; Miyasaka et al. 2006), but it is estimated that prevalence will increase to approximately 12.1 million in 2030 (Colilla et al. 2013). AF is associated with an increased risk of mortality, including mortality attributable to CVD and non-CVD causes (Benjamin et al. 2017).

Zhu and colleagues (2016) found in a meta-analysis of 16 prospective studies (286,217 patients and 11,878 cases of AF) that cigarette smoking was associated with a higher risk of AF (RR = 1.23; 95% CI, 1.08–1.39). Findings on AF related to current, former, and never smokers were available from 8 of the 16 studies. Former smokers had 1.16 times the risk of AF (95% CI, 1.00–1.36), and current smokers had 1.39 times the risk (95% CI, 1.11–1.36) compared with never smokers. Time since cessation was not assessed in any of the studies. Among persons with AF, smoking has also been associated with an increased risk of adverse events (Albertsen et al. 2014; Kwon et al. 2016). In the cohorts of the ARIC study and the Cardiovascular Health Study, current, but not former, smoking was associated with an increased risk of CVD deaths or ischemic stroke among persons with AF (Kwon et al. 2016). In the Danish Diet and Cancer study, former smoking was associated with an increased risk of thromboembolism or death among women with AF but not among men with AF (Albertsen et al. 2014).

Summary of the Evidence

A meta-analysis found that current and former cigarette smoking is associated with a higher risk of AF than never smoking, and the pooled estimate for former smokers was lower than that for current smokers. Findings from other studies regarding AF-related adverse events are mixed. No additional evidence is currently available on how the risk of AF changes with smoking cessation or with time since cessation.

Smoking Cessation and Sudden Cardiac Death

Cardiac arrest is the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation (Jacobs et al. 2004). Although it is a leading cause of death, the absence of nationwide surveillance standards makes it difficult to understand the epidemiology of cardiac arrest in the United States (Benjamin et al. 2017). Sudden cardiac death (SCD) is an unexpected death without an obvious noncardiac cause that occurs, if witnessed, within 1 hour of symptom onset or, if not witnessed, within 24 hours of the person's last being observed in normal health, although it is challenging to apply these criteria in practice (Benjamin et al. 2017). SCD can be attributable to cardiac or noncardiac causes; it is usually presumed to be attributable to cardiac causes unless another explanation can be identified. Based on the Resuscitation Outcomes Consortium registry of all emergency management system (EMS)-attended calls in 2015 for out-of-hospital cardiac arrests in eight U.S. and three Canadian regions, the incidence of out-of-hospital cardiac arrests assessed by EMS was estimated to be 110.8 persons per 100,000 (95% CI, 108.9–112.6) (Benjamin et al. 2019). Based on this registry, the rate of survival to hospital discharge for EMS-treated out-of-hospital cardiac arrest was 11.4% (95% CI, 10.4–12.4%) in adults, and survival after bystander-witnessed ventricular fibrillation was 37.4% (95% CI, 32.7–42.0%) for patients of any age (Benjamin et al. 2017).

The 2014 Surgeon General's report reviewed epidemiologic evidence from several studies showing that cigarette smoking is associated with SCD of all types. During 30 years of follow-up of 101,018 women without known CHD, stroke, or cancer at the 1980 baseline in the Nurses' Health Study, there were 351 SCD events, of which 148 occurred in former smokers (Sandhu et al. 2012). Overall, compared with never smokers, the adjusted hazard of SCD was higher among current smokers (HR = 2.44; 95% CI, 1.80–3.31) and former smokers (HR = 1.40; 95% CI, 1.10–1.79). Compared with current cigarette smokers, former smokers had a lower risk of SCD (HR = 0.58; 95% CI, 0.43–0.77). The risk of SCD decreased linearly over time after quitting smoking (p for trend <0.0001). After 15 years of cessation, the risk was significantly lower in former smokers than in current smokers; after 20 years of cessation, the risk was similar in former smokers and never smokers. In analyses stratified by CHD status, women with CHD who quit smoking tended to have a higher risk of SCD than never smokers, while increased risk of SCD dropped within 5 years and did not decline further among those who quit and did not have CHD (p-value interaction = 0.15). Among women who quit,

those without CHD had a more rapid reduction in SCD risk than those with CHD (p-value interaction = 0.03).

Similar findings have been observed among populations with known CHD (Vlietstra et al. 1986; Peters et al. 1995; Goldenberg et al. 2003) or with prior cardiac arrest (Hallstrom et al. 1986). For example, among 3,122 patients with previous MI or stable angina, smoking was associated with an increased risk of SCD, and those who quit smoking had a decreased risk of SCD (Goldenberg et al. 2003). Compared with never smokers (43 cases of SCD), current smokers had 2.47 times (95% CI, 1.46–4.49, 30 cases) the adjusted risk of SCD, while former smokers did not have an elevated adjusted risk (HR = 1.06; 95% CI, 0.70–1.62, 83 cases).

In a study of data from the CALIBER program in England, which uses electronic health records, there was no pattern of decreased age-adjusted risk of cardiac arrest or SCD with increasing time since smoking cessation (not shown) (Pujades-Rodriguez et al. 2015). In this study, however, current smoking also was not associated with increased hazard of this outcome compared with never smoking; the section on CHD discusses concerns about the validity of this study.

Summary of the Evidence

Several studies show that smoking cessation is associated with a reduced risk of SCD. The majority of these studies were carried out among patients with prior CHD. A large study in women found a similar association; however, among those with and without CHD, results show a quicker benefit from smoking cessation among those without known CHD. In this study, the risk of SCD returned to that of never smokers after approximately 20 years of cessation.

Smoking Cessation and Heart Failure

Heart failure results from the inability of the heart to pump sufficient blood and deliver enough oxygen to support other organs in the body. An estimated 6.5 million U.S. adults have heart failure (Benjamin et al. 2017); in 2014, heart failure was mentioned on the death certificate for one in every eight deaths (Benjamin et al. 2017; National Center for Health Statistics 2017). Approximately half of those with heart failure die within 5 years of diagnosis (Roger et al. 2004; Benjamin et al. 2017). In 2012, heart failure cost the United States an estimated $30.7 billion in direct and indirect costs; this figure is projected to increase to $69.8 billion by 2030 (Heidenreich et al. 2013). The prevalence of heart failure is projected to increase to approximately 46% by 2030; thus, more than 8 million persons 18 years of age or older are expected to have heart failure in that year (Heidenreich et al. 2013).

The 1990 Surgeon General's report did not address smoking cessation and risk for heart failure. The 2004 Surgeon General's report suggested that CHD caused by smoking may contribute to heart failure and that this contribution is likely mediated by CHD (USDHHS 2004). Regardless, the pathophysiologic mechanisms underlying the development of heart failure overlap with the effects of cigarette smoking on the cardiovascular system (Suskin et al. 2001). This section briefly reviews the literature on smoking cessation and the development and prognosis of heart failure.

Ahmed and colleagues (2015) reported on the relationships in the Cardiovascular Health Study between prolonged smoking cessation (>15 years) and risk of heart failure and death among 4,482 adults 65 years of age or older who were free of heart failure at baseline. During the 13-year follow-up, former smokers had risks for incident heart failure (adjusted HR = 0.99; 95% CI, 0.85–1.16) and all-cause mortality (adjusted HR = 1.08; 95% CI, 0.96–1.20) that were similar to those of never smokers (Table 4.18). In another cohort study of older adults, both current and former smokers had elevated risk of heart failure compared with the risk among never smokers (Table 4.18) (Gopal et al. 2012).

In the Cardiovascular Health Study, compared with never smokers, former heavy smokers (≥32 pack-years) had a higher risk of heart failure (multivariable-adjusted HR = 1.31; 95% CI, 1.03–1.65) and mortality (multivariable-adjusted HR = 1.26; 95% CI, 1.06–1.49 [not shown in table]) (Ahmed et al. 2015). Compared with current smokers, however, former heavy smokers had a lower risk of mortality (age-, sex-, and race-adjusted HR = 0.64; 95% CI, 0.53–0.77) but not of heart failure (age-, sex-, and race-adjusted HR = 0.97; 95% CI, 0.74–1.28). Overall, this study found that after prolonged smoking cessation the risk of heart failure was similar between former smokers and never smokers, but not for former heavy smokers with cumulative consumption of 32 or more pack-years.

In the CALIBER program in England, the age-adjusted HR for heart failure decreased with increased time since smoking cessation (Table 4.18); 2 years after cessation, the age-adjusted hazard of heart failure was not elevated compared with never smokers (not shown in table) (Pujades-Rodriguez et al. 2015). In a study of 267,010 Australian men and women 45 years of age or older with self-reported smoking status that had been linked to administrative hospital data, former smokers and current smokers had a higher adjusted hazard of heart failure hospitalization compared with never smokers (Tran et al. 2015). Risks of hospitalization for heart failure decreased

Table 4.18 Observational studies on smoking cessation and heart failure (incident heart failure and heart failure-related complications)

Study	Design/population	Findings: RR (95% CI)	Comments
Suskin et al. (2001)[a]	• Prospective cohorts (observational analyses of two multicenter trials included in the Study of Left Ventricular Dysfunction Prevention and Intervention) • 6,704 participants with left ventricular ejection fraction <35% but no history of overt congestive heart failure, mean 60 years of age, 86% men, predominantly White but also African American and other races/ethnicities, 55% former smokers • Years of data collection: not provided • Belgium, Canada, and United States • Mean follow-up: 41 months (treatment trial) and 37 months (prevention trial) • Main outcome: total mortality	• Total mortality: – Never smoker: 1.00 (referent) – Former smoker (quit ≤2 years): 1.10 (0.94–1.29) – Former smoker (quit >2 years): 0.95 (0.82–1.09) – Current smoker: 1.40 (1.21–1.63) • Similar results for mortality from congestive heart failure, hospitalization for congestive heart failure, hospitalization for MI, and mortality or hospitalization because of congestive heart failure or MI	—
Shah et al. (2010)[a]	• Prospective cohort (observational analyses of Survival and Ventricular Enlargement trial) • 924 patients with left ventricular dysfunction 3–16 days after MI, restricted to smokers at baseline who survived to 6 months without interim event, 82% men, 54 years of age (mean), 63% quit smoking, 85 deaths • Years of data collection: not provided • United States • Median follow-up: 42 months • Main outcome: death	• Total mortality: – Current smoker: 1.00 (referent) – Former smoker (months of consistent cessation[b]): ○ 6: 0.57 (0.36–0.91) ○ 12: 0.58 (0.33–0.99) ○ 16: 0.60 (0.34–1.07) ○ 24: 0.53 (0.25–1.08) • Similar results for outcomes of death or recurrent MI and death or hospitalization for heart failure • Similar trend of decreased risk at 6 months of cessation for endpoint of death or recurrent MI, hospitalization for heart failure, or stroke	—

Table 4.18 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Gopal et al. (2012)[a]	• Prospective cohort (Health, Aging, and Body Composition Study) • 2,125 participants, 70–79 years of age (mean: 73.6 years), 30% men, Whites and African Americans, 35% former smokers, all Medicare beneficiaries and without prevalent heart failure, 231 cases of heart failure • Recruited in 1997–1998 • United States • Median follow-up: 9.4 years • Outcome: heart failure	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker (overall): 1.31 (0.98–1.75) – Current smoker (overall): 1.73 (1.15–2.59) • Smoking intensity (number of pack-years[c]): – Never smoker: 1.00 (referent) – Former smoker: ○ 1–11: 1.05 (0.64–1.72) ○ 12–35: 1.23 (0.82–1.83) ○ >35: 1.64 (1.11–2.42) – Current smoker: ○ 1–11: 1.92 (0.76–4.88) ○ 12–35: 1.67 (0.89–3.15) ○ >35: 1.71 (0.97–3.01)	—
Ahmed et al. (2015)[a]	• Prospective cohort (Cardiovascular Health Study) • 4,482 participants, ≥65 years of age, 40% men, multiple races/ethnicities (Whites, African Americans, others), 29% former smokers who quit >15 years earlier without prevalent heart failure, 1,204 cases of heart failure • 1989–1993 (baseline) • United States (four counties) • Follow-up: 13 years • Main outcome: heart failure	• Former smokers restricted to those who had quit >15 years • Smoking status: – Never smoker: 1.00 (referent) – Former smoker (overall): 1.07 (0.91–1.25) – Current smoker (overall): 1.19 (0.99–1.44) • Smoking intensity (number of pack-years[c]): – Never smoker: 1.00 (referent) – Former smoker: ○ <8: 1.06 (0.83–1.36) ○ 8–15: 0.86 (0.62–1.20) ○ 16–31: 0.99 (0.77–1.28) ○ ≥32: 1.31 (1.03–1.65) • Similar results for outcome of mortality, but stronger association for current smokers: – 2.17 (1.91–2.47)	—

Table 4.18 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Pujades-Rodriguez et al. (2015)[a]	• Prospective cohort • 1.93 million participants; ≥30 years of age; 49% men, predominantly White (also South Asian and Black), and 16.2% former smokers (among those with smoking data); drawn from CALIBER program (linked electronic health records); no history of CVD; 4,097 cases of heart failure in former smokers • 1997–2010 • England • Median follow-up: 6 years	• Heart failure by smoking status (age-adjusted): – Current smoker: 1.00 (referent) – Former smoker (years since quitting): ○ <2: 0.87 (0.60–1.26) ○ 2–9: 0.72 (0.52–0.99) ○ >10: 0.60 (0.44–0.81)	See Table 4.17 for concerns about validity

Notes: **CALIBER =** Clinical research using LInked Bespoke studies and Electronic health Records; **CI =** confidence interval; **CVD =** cardiovascular disease; **MI =** myocardial infarction; **RR =** risk ratio.

[a]Measure(s) of association adjusted for covariate(s).

[b]Duration of consistent smoking cessation after MI, compared with continuation of smoking, among those who were stable baseline smokers and survived up to that time without recurrent MI or hospitalization for heart failure.

[c]Pack-years = number of packs of cigarettes smoked per day multiplied by the number of years smoked cigarettes.

with increased time since quitting; the decrease was substantially different between current and former smokers after 25 or more years of cessation.

In their analyses of data from 4,850 elderly participants free of overt CHD, heart failure, and significant valvular disease in the ARIC study, Nadruz and colleagues (2016) found that, after adjusting for potential confounders, current smokers had a greater left-ventricular mass index and left-ventricular mass/volume ratio, a higher prevalence of left-ventricular hypertrophy, and worse diastolic function than never smokers. In contrast, former smokers showed echocardiographic features similar to those of never smokers.

Other researchers have assessed the relationship between smoking cessation and elevated risk of complications related to heart failure and found associations between cessation and decreased risk of hospitalization for or mortality from heart failure and other adverse events. For example, the prevention and intervention trials of the Study of Left Ventricular Dysfunction studied 6,704 persons with a left ventricular ejection fraction <0.35 with or without symptoms of congestive heart failure. Compared with never smokers (Table 4.18), former smokers had no difference in adjusted risk of overall mortality, mortality from congestive heart failure, hospitalization for congestive heart failure, hospitalization for MI, or risk of mortality or hospitalization due to congestive heart failure or MI (Suskin et al. 2001). Risks were similar in those who had stopped smoking for 2 or fewer years and those who had quit more than 2 years earlier. In contrast, continued smoking was associated with higher risk of overall mortality, hospitalization for congestive heart failure, hospitalization for MI, and mortality or hospitalization due to congestive heart failure or MI. Suskin and colleagues (2001) concluded that smoking cessation was associated with a rapid decrease in risk of morbidity and mortality among these participants. The reduction in mortality was similar in magnitude to the decrease from (a) the appropriate use of an angiotensin-converting enzyme inhibitor or beta-adrenergic blocking agents, or (b) all commonly used treatments of spironolactone among patients with reduced left ventricular systolic function and symptoms of congestive heart failure.

In the Survival and Ventricular Enlargement trial involving patients with left ventricular dysfunction after MI, 924 participants were stable smokers at baseline. Among those who survived to 6 months without a recurrent event, those who had quit for 6 months had a lower risk of death than those who continued to smoke (Table 4.18) (Shah et al. 2010). Similar patterns were observed during follow-up at 12, 16, and 24 months and for composite endpoints (death or hospitalization for heart failure; death or recurrent MI). At 6 months of cessation after an MI, there was a similar trend toward lower risk for the combined endpoint of death, MI, hospitalization for heart failure, or stroke (adjusted HR = 0.72; 95% CI, 0.52–1.01). Earlier, in a cohort of 4,024 patients receiving dialysis, the rate of new-onset congestive heart failure (based on hospital claims data) was similar in former smokers and never smokers (Foley et al. 2003). These findings indicate the importance of smoking cessation among persons who are at elevated risk for complications related to heart failure (Suskin et al. 2001; Shah et al. 2010).

Summary of the Evidence

There is limited evidence that smoking cessation is associated with a reduced risk of incident heart failure and adverse events related to heart failure.

Smoking Cessation and Venous Thromboembolism

The term "venous thromboembolism" (VTE) refers to a blood clot that forms in a vein; an embolism occurs when the clot breaks free. The incidence of VTE in the United States has been estimated to be approximately 300,000 to 600,000 per year (Silverstein et al. 1998; White et al. 2005; Spencer et al. 2006), but these estimates are based on older data (Benjamin et al. 2017). A systematic review and meta-analysis (covering 1980–2013) found that, compared with never smoking, current smoking (RR = 1.23; 95% CI, 1.14–1.33; 15 studies) and former smoking (RR = 1.10; 95% CI, 1.03–1.17; 14 studies) are associated with an increased risk of incident VTE (Cheng et al. 2013). This study did not evaluate the association between time since smoking cessation and risk of VTE.

Summary of the Evidence

A meta-analysis showed that current and former cigarette smokers have an increased risk of VTE when compared with never smokers, and the RR for former smokers is lower than that for current smokers. There is no evidence available on how the risk of VTE changes with time since cessation.

Smoking Cessation and Lower-Extremity Peripheral Artery Disease

Peripheral artery disease (PAD) results from the narrowing (usually due to atherosclerosis) of the peripheral arteries leading to the legs, abdominal organs, arms, and head. This disorder most commonly affects the arteries

of the legs. The presence of PAD of the lower limbs can be detected by measuring the ABI, which is the ratio of blood pressure in the lower leg to that in the upper arm (as discussed in the earlier section on smoking cessation and subclinical atherosclerosis). Importantly, a low ABI does not indicate which blood vessels are narrowed or blocked. Approximately 8.5 million people in the U.S. have PAD (CDC 2016a). One symptom of PAD is intermittent claudication, or leg cramping induced by exercise (also known as classic claudication). An estimated 10% of persons with PAD have intermittent claudication, approximately 40% have no leg pain, and 50% have other leg symptoms (Hirsch et al. 2001; Benjamin et al. 2017). PAD leads to impaired function and reduces quality of life. Further, PAD is a systemic atherosclerotic disease, and is therefore a risk factor for poor clinical outcomes, including CHD and stroke (Heald et al. 2006; Benjamin et al. 2017).

The 1983 Surgeon General's report concluded that cigarette smoking is the most powerful risk factor predisposing men and women to atherosclerotic peripheral vascular disease (USDHHS 1983). According to the 2004 Surgeon General's report, the evidence is sufficient to infer a causal relationship between smoking and atherosclerosis (USDHHS 2004), as discussed earlier in this section. The 2004 Surgeon General's report concluded that "the new findings on subclinical disease indicate the potential for preventing more advanced and clinically symptomatic disease through quitting smoking and maintained cessation" (USDHHS 2004, p. 379).

The 1990 Surgeon General's report discussed results from two small studies comparing the risk of PAD between smokers and former smokers, finding that former smokers had a 50–58% lower risk of PAD than current smokers (Hughson et al. 1978; Jacobsen et al. 1984). Several studies of persons with PAD found that those who quit smoking had improved performance and overall survival. Since 1990, the literature on this topic has grown substantially, as reviewed in the next two sections.

A meta-analysis conducted by Lu and colleagues (2014) quantified the association between active smoking and PAD. This meta-analysis, which was restricted to studies examining the risk of developing PAD, defined PAD on the basis of an ABI ≤0.90, a claudication questionnaire, or peripheral angiography. Although the risk of PAD was lower for former smokers than for current smokers, the risk of PAD in both groups was still significantly higher than that for never smokers. Compared with nonsmokers, current smokers had 2.71 times the pooled odds of PAD (95% CI, 2.28–3.21). As shown in Figure 4.3, there were 40 estimates in this meta-analysis (Lu et al. 2014) of the risk of PAD gathered from 29 studies of former smokers compared with never smokers. Of the 40 estimates, 29 (72.5%) were statistically significant, and the pooled OR comparing former with never smokers was 1.67 (95% CI, 1.54–1.81). This estimate included studies of the general population, as well as studies of persons with underlying diseases, such as diabetes mellitus.

Lu and colleagues (2014) identified two studies (Törnwall et al. 2000; Cui et al. 2006) that compared risk of PAD between former and current smokers and found a reduced risk of PAD among former smokers. In the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, among a cohort of 26,872 male smokers who were 50–69 years of age at entry, the HR of PAD during a median follow-up of 4 years in former smokers was 0.86 (95% CI, 0.75–0.99) compared with the HR among current smokers (Törnwall et al. 2000). As this study did not include never smokers, its results were not included in the pooled estimate reported by Lu and colleagues (2014). In the report by Cui and colleagues (2006) on a cross-sectional study of 1,215 elderly Japanese men, those authors found that, compared with current smokers, there was no significant difference in the odds of PAD (ABI <0.90) after less than 10 years of smoking cessation (OR = 0.8; 95% CI, 0.4–1.8) or after 10–19 years of cessation (OR = 1.0; 95% CI, 0.4–2.2) (Cui et al. 2006). The risk of PAD was reduced, however, among those who had quit smoking for 20 or more years (OR = 0.3; 95% CI, 0.1–0.9).

The meta-analysis by Lu and colleagues (2014) focused on publications that reported ORs or RRs, and it treated RRs as ORs. Several other key articles on this topic that were not included in the meta-analysis—because of a restriction or publication after the literature search or for another reason—are described below.

Fowkes and colleagues (1992) reported that lifetime cumulative cigarette smoking was strongly related to risk of PAD, with additional risks among current and former smokers abstinent less than 5 years. Elsewhere, in a cohort of Icelandic men, when compared with never smoking, former smoking was associated with having 3.5 times the odds of prevalent intermittent claudication and 2.3 times the odds of incident intermittent claudication during follow-up from 1968 to 1986; neither of these ORs was significant (Ingolfsson et al. 1994). Among smokers, those who smoked 15 or more cigarettes per day had a higher risk of incident intermittent claudication. In a later study, Foley and colleagues (2003) reported that in a cohort of 4,024 patients receiving dialysis, former smokers had an adjusted rate of peripheral vascular disease similar to that of lifelong nonsmokers. In a prospective cohort study of 39,825 initially healthy women from the Women's Health Study, Conen and colleagues (2011) reported that smoking cessation substantially reduced the risk of symptomatic PAD, but former smokers still had an excess risk of PAD compared with never smokers. Compared with

Figure 4.3 Comparison of risk of peripheral arterial disease between former and never smokers

Study	Estimate (95% CI)	Weight (%)[a]
General population		
Skalkidis et al. 1989 (MF)	2.30 (0.40–15.20)	0.19
Bowlin et al. 1994 (M)	1.43 (1.05–1.95)	3.37
Leng et al. 1995 (MF)	2.15 (1.21–3.82)	1.53
Ögren et al. 1996 (M)	3.10 (1.40–6.90)	0.90
Hooi et al. 1998 (asymptomatic) (MF)	1.60 (1.10–2.40)	2.62
Hooi et al. 1998 (symptomatic) (MF)	2.70 (1.40–5.40)	1.19
Meijer et al. 2000 (MF)	1.15 (0.75–1.78)	2.30
Passos et al. 2001 (MF)	3.10 (1.20–8.50)	0.62
Fowler et al. 2002a (M)	2.10 (1.60–2.60)	4.16
Jensen et al. 2005 (F)	1.70 (1.10–2.70)	2.19
Jensen et al. 2005 (M)	1.70 (0.90–3.20)	1.31
Zheng et al. 2005 (African M)	6.60 (2.00–21.50)	0.44
Zheng et al. 2005 (African F)	2.30 (1.50–3.50)	2.36
Zheng et al. 2005 (White M)	10.40 (3.80–28.30)	0.59
Zheng et al. 2005 (White F)	1.90 (1.40–2.60)	3.37
Kennedy et al. 2005 (MF)	1.32 (0.94–1.87)	3.02
He et al. 2006 (stop 2–9 years) (M)	1.74 (1.01–2.98)	1.68
He et al. 2006 (stop ≥10 years) (M)	1.18 (0.68–2.03)	1.65
He et al. 2006 (stop 2–9 years) (F)	1.27 (0.59–2.73)	0.96
He et al. 2006 (stop ≥10 years) (F)	0.93 (0.37–2.31)	0.70
Woo et al. 2006 (MF)	2.00 (1.18–3.38)	1.75
Bendermacher et al. 2007 (MF)	1.40 (1.20–1.60)	5.48
Agarwal et al. 2009 (MF)	1.55 (1.16–2.08)	3.57
Cacoub et al. 2009 (>1 year) (MF)	1.38 (1.15–1.66)	4.95
Cacoub et al. 2009 (≤1 year) (MF)	2.48 (1.79–3.42)	3.22
Kröger et al. 2009 (MF)	1.99 (1.44–2.75)	3.23
Alzamora et al. 2010 (MF)	2.19 (1.34–3.58)	1.93
Lakshmanan et al. 2010 (M)	2.03 (1.39–2.98)	2.69
St-Pierre et al. 2010 (M)	1.14 (0.59–2.21)	1.23
Aboyans et al. 2011 (MF)	1.39 (0.97–1.97)	2.93
Lee et al. 2011 (M)	2.31 (1.20–4.42)	1.26
Subtotal (I-squared = 52.3%, p = 0.000)	1.76 (1.58–1.97)	67.40

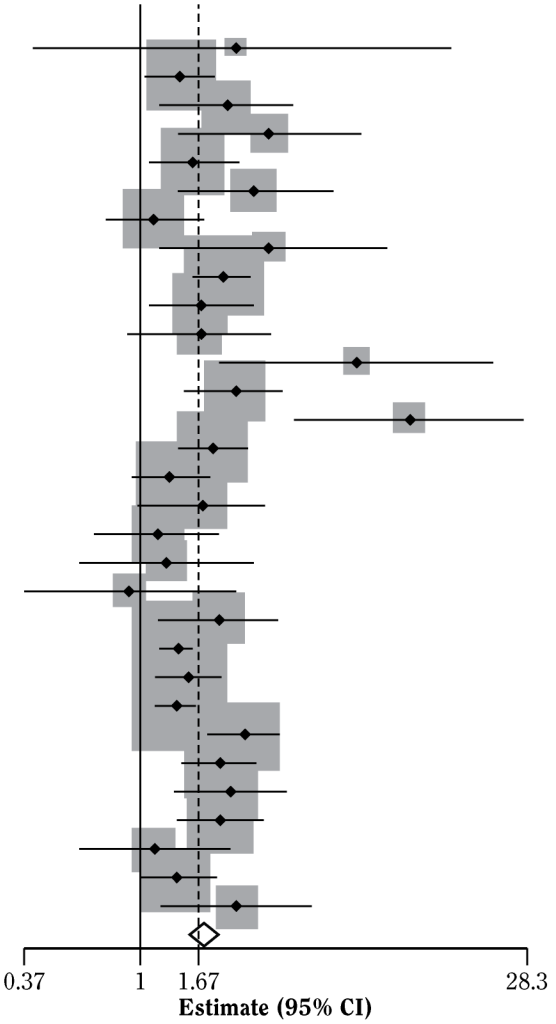
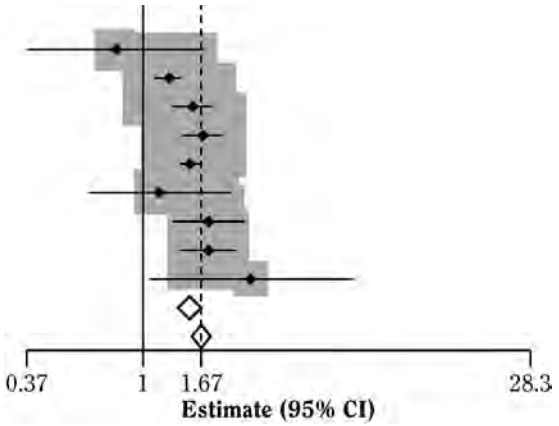


Figure 4.3 Continued

Study	Estimate (95% CI)	Weight (%)[a]
Disease study population		
Adler et al. 2002 (DM) (MF)	0.80 (0.37–1.72)	0.95
O'Hare et al. 2002 (hemodialysis) (wave 3, 4) (MF)	1.27 (1.13–1.42)	5.85
O'Hare et al. 2002 (hemodialysis) (wave 1) (MF)	1.55 (1.31–1.83)	5.17
Rajagopalan et al. 2006 (<1 year) (hemodialysis) (MF)	1.68 (1.41–2.01)	5.03
Rajagopalan et al. 2006 (>1 year) (hemodialysis) (MF)	1.51 (1.38–1.65)	6.13
Norman et al. 2006 (DM) (MF)	1.16 (0.62–2.15)	1.36
Li et al. 2007 (DM) (MF)	1.79 (1.30–2.46)	3.27
Luo et al. 2007 (HT) (MF)	1.79 (1.40–2.29)	4.10
Tavintharan et al. 2009 (DM) (MF)	2.55 (1.05–6.20)	0.74
Subtotal (I-squared = 54.0%, p = 0.026)	1.52 (1.36–1.69)	32.60
Overall (I-squared = 54.7%, p = 0.000)	1.67 (1.54–1.81)	100.00



Source: Lu et al. (2014), with permission.

Note: **CI =** confidence interval; **DM =** diabetes mellitus; **F =** females; **HT =** hypertension; **M =** males; **MF =** males and females.

[a]Weights are from random effects analysis.

current smokers, the adjusted HR of symptomatic PAD among former smokers was 0.39 (95% CI, 0.24–0.66) for less than 10 years of cessation, 0.28 (95% CI, 0.17–0.46) for 10–20 years of cessation, and 0.16 (0.10–0.26) for more than 20 years of cessation. Compared with never smokers, the adjusted HR of symptomatic PAD among former smokers was 3.16 (95% CI, 2.04–4.89).

In the CALIBER program, the age-adjusted HR of PAD decreased substantially with increased time since smoking cessation (Pujades-Rodriguez et al. 2015). Compared with current smokers, former smokers who had quit for more than 10 years had an age-adjusted HR for PAD of 0.27 (95% CI, 0.22–0.33). Compared with women who had never smoked, however, the age-adjusted hazard of PAD was still elevated significantly in women who had quit smoking for 10 or more years (HR = 1.36; 95% CI, 1.11–1.67).

Smoking has also been associated with other forms of PAD, such as Raynaud's disease or syndrome, which is a form of functional PAD that begins with severe vasoconstriction followed by dilatation (widening of the blood vessels) not due to blockage. Various studies have associated current smoking with Raynaud's, with a stronger association evident in men than in women. In the Framingham Offspring cohort, former smokers did not have an elevated risk of Raynaud's compared with never smokers (Brand et al. 1997; Suter et al. 2007). Smoking cessation is recommended for persons with Raynaud's, because the vasoconstrictive substances in cigarettes likely make the condition worse (Pope 2007). The IARC's (2007) review on smoking cessation found consistent evidence from a number of small case series that smoking cessation was associated with improved thromboangiitis obliterans (Buerger's disease), which is an inflammatory, obliterative disease that affects small- and medium-sized arteries, is unrelated to atherosclerosis, and is specific to smokers. Later, Klein-Weigel and colleagues (2016) concluded that smoking cessation is the most important intervention among patients with Buerger's disease.

Prognosis of PAD

In addition to its association with the onset of PAD, smoking or the continuation of smoking after a PAD diagnosis is a major risk factor for the progression of PAD and PAD-related outcomes (Jonason and Ringqvist 1985; Ameli et al. 1989; Wiseman et al. 1989; Selvarajah et al. 2014). Correspondingly, current clinical guidelines recommend smoking cessation among patients with PAD (Olin et al. 2010; Rooke et al. 2011; Smith Jr et al. 2011; Tendera et al. 2011; Gerhard-Herman et al. 2017).

A systematic review that assessed the effects of clinical interventions for persons with chronic PAD (based on literature searched through 2005) concluded that smoking cessation combined with exercise may increase walking distance (Cassar and Bachoo 2006). This conclusion was based on a randomized controlled study that assessed the impact of a "stop smoking and keep walking" intervention compared with usual care among 882 Australian men 65–79 years of age who had early PAD (Fowler et al. 2002b). Specifically, the intervention combined a community-based intervention of smoking cessation (where applicable) with increased physical activity. At 12 months, a higher proportion of men in the intervention group had an improved maximum walking distance compared with those in the usual-care group (23% vs. 15%, p = 0.008). In addition, compared with the control group, more men in the intervention group reported walking more than three times per week for recreation (34% vs. 25%, p = 0.01). Also, although the finding was not statistically significant, more men in the intervention group had stopped smoking (12% vs. 8%, p = 0.43).

A systematic review of smoking cessation and prognosis for PAD based on a 1996 search (Girolami et al. 1999) summarized some of the findings reported in the 1990 Surgeon General's report (USDHHS 1990). Most of the findings showed that smoking cessation was associated with favorable outcomes. A study of 415 smokers with intermittent claudication and an ABI <0.9, however, found no difference in deterioration of the ABI at 1 year between current smokers and former smokers (Smith et al. 1996). Of note, this analysis adjusted only for diabetes status; former smokers were more likely than current smokers to have diabetes.

In a registry of 467 stable outpatients who smoked and had symptomatic PAD, those who quit smoking had, during a mean follow-up of 14 months, a nonadjusted relative risk of death of 1.83 (95% CI, 0.65–5.15) compared with continuing smokers (Álvarez et al. 2013). This study was limited by the small number of events, however, making it challenging to draw conclusions. In an earlier study, among 138 patients with peripheral arterial occlusive disease, a subgroup of 38 patients who had smoked an average of 1.5 packs of cigarettes per day for more than 42 years had more severe claudication pain, lower oxygen uptake at peak exercise, and a higher oximeter electrode power than a subgroup of 100 patients who had quit smoking for an average of 7 years (Gardner 1996). Results were similar after adjusting for baseline ABI. In a later study of 204 patients with claudication or critical limb ischemia who had undergone lower-extremity angiography, smoking cessation was associated with a lower 5-year adjusted HR of mortality (HR = 0.33; 95% CI, 0.13–0.80) and improved amputation-free survival (HR = 0.40; 95% CI, 0.19–0.83) compared with those who continued to smoke (Armstrong et al. 2014). Nonsignificant HRs were observed in this study for MI, stroke, and major

amputation (there were few cases of these outcomes); a nonsignificant HR in the opposite direction was observed for major adverse limb events.

Summary of the Evidence

There is evidence that former cigarette smokers have a lower risk of incident PAD than current smokers and that the risk of PAD decreases with increased time since smoking cessation. Compared with never smokers, former smokers typically have an increased risk of PAD. Despite few large prospective cohort studies assessing these associations, evidence suggests that smoking cessation is associated with improved prognosis among persons with PAD.

Smoking Cessation and Abdominal Aortic Aneurysm

An aortic aneurysm is a ballooning or bulging area on the aorta wall, which can lead to rupture or dissection (a split between the layers of the wall of the aorta, thus trapping blood) (American Heart Association 2017). The prevalence of abdominal aortic aneurysms (AAAs) extending 2.9–4.9 centimeters (cm) among men has been estimated to be 1.3% in those 45–54 years of age and 12.5% in those 75–85 years of age; the prevalence among women has been estimated at 0% (45–54 years of age) and 5.2% (75–85 years of age) (Hirsch et al. 2006). These estimates, however, came predominantly from cohorts of White men and women. Ruptures in patients with AAA are more common in current smokers (a doubling of risk) and among women (almost four times the risk) (Sweeting et al. 2012).

According to the 2004 Surgeon General's report, the evidence is sufficient to infer a causal relationship between smoking and AAA (USDHHS 2004). That report stated that "smoking is one of the few currently avoidable causes of this frequently fatal disease" (p. 397). According to the 1990 Surgeon General's report (USDHHS 1990), former smokers have a reduced risk of death from aortic aneurysm compared with current smokers, but the report noted that more detailed analyses by duration of smoking abstinence are needed. The 1990 report did not provide any formal conclusions about smoking cessation and AAA.

The 1990 report discussed results from five prospective cohort studies that compared risk of death from AAA between former smokers and current smokers. Overall, in men there was a consistent pattern of a reduced risk of death from AAA among former smokers compared with current smokers. At the time, evidence was more limited in women. Since publication of the 1990 report, many additional studies have been published on this topic, as summarized below and in Table 4.19.

In 1999, a literature review concluded that smoking was strongly associated with AAA (Blanchard 1999). Some of the studies in this review examined associations with this outcome between former smokers and never smokers. For example, during 40 years of follow-up of the British Doctors' Study, the rate of death from non-syphilitic AAA (standardized for age and calendar period) was more than four times as high among current smokers and more than twice as high among former smokers as among never smokers (CIs not provided) (Doll et al. 1994). In the Cardiovascular Health Study of older Americans, the prevalence of AAA was 6.8% for never smokers, 11.5% for former smokers, and 14.4% for current smokers (Alcorn et al. 1996).

Several observational studies published in 1997 or later have assessed the relationship between smoking cessation and the incidence or prevalence of AAA. Overall, the evidence suggests that smoking cessation is associated with a decreased risk of AAA (Lederle et al. 1997, 2000, 2003; Wilmink et al. 1999; Singh et al. 2001; Wong et al. 2007; Forsdahl et al. 2009; Kent et al. 2010; Stackelberg et al. 2014; Tang et al. 2016). Even so, compared with never smokers, former smokers tend to have an increased risk of AAA that can persist for decades after quitting (Wong et al. 2007).

Findings from observational studies on cessation and AAA are summarized in Table 4.19. For example, in two cohorts of veterans undergoing screening in the Aneurysm Detection and Management study, the OR for AAA (diameter ≥4.0 cm) among former smokers compared with current smokers was 0.73 (95% CI, 0.66–0.82) for every 10 years of smoking cessation (Lederle et al. 1997, 2000). In addition, after accounting for number of years smoked, risk of AAA was higher in current smokers than in former smokers (Table 4.19). In a later study, in a large cohort of patients who underwent ultrasound screening for AAA, former smokers had a lower prevalence of AAA than current smokers, and risk decreased as duration of cessation increased from less than 5 years to more than 10 years (Kent et al. 2010). Similar patterns of decreasing risk as duration of cessation increased were observed in other studies (Wong et al. 2007; Stackelberg et al. 2014; Tang et al. 2016).

According to data from 2002 from CPS II that was reported in the 2004 Surgeon General's report, mortality attributable to AAA was significantly higher among men and women who were current smokers compared with never smokers (USDHHS 2004). Risk of mortality due to AAA was lower in former smokers than in current smokers but was higher in former smokers than in never smokers. Pujades-Rodriguez and colleagues (2015), in their analysis of data from the CALIBER program, reported that the age-adjusted HR of AAA tended to decrease with increased

Table 4.19 Observational studies on smoking cessation and abdominal aortic aneurysm

Study	Design/population	Findings: RR (95% CI)	Comments
Lederle et al. (1997, 2000)[a]	• Cross-sectional analyses (Aneurysm Detection and Management) • Two cohorts of veterans, 50–79 years of age, 97% men, 87% White (also African American and other races/ethnicities), no history of AAA • Sample sizes and number of AAAs (≥3.0 cm): – Cohort 1: n = 73,451; 3,366 AAAs – Cohort 2: n = 52,745; 1,917 AAAs • Screened in 1992–95 and 1995–97, respectively • United States	• Cohort 1: – AAA 3.0–3.9 cm diameter ○ Current smoker: 1.00 (referent) ○ Former smoker (per 10 years since quitting): 0.81 (0.76–0.86) – AAA ≥4.0 cm diameter ○ Current smoker: 1.00 (referent) ○ Former smoker (per 10 years since quitting): 0.72 (0.65–0.79) • Cohort 2: similar findings	—
Wilmink et al. (1999)[a]	• Nested case-control study • Men, >50 years of age, 210 cases of AAA (>29 cm) from AAA screening study, 237 age-matched controls, 64% of cases and 63% of controls were former smokers • Years of data collection: not provided • Huntingdon, United Kingdom	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 4.0 (1.7–9.5) – Current smoker: 9.0 (3.4–24.0) – Similar results when reclassified based on cotinine level • Years since quitting: – Current smoker: 1.00 (referent) – Former smoker ○ 1–5: 0.62 (0.2–1.7) ○ 6–10: 0.47 (0.2–1.3) ○ 11–20: 0.61 (0.3–1.3) ○ 21–30: 0.28 (0.1–0.7) ○ ≥30 years: 0.20 (0.1–0.4) – When also adjusted for duration of smoking, results trended toward weaker associations	Adjusting for duration of smoking in the time-since-quitting analysis might lead to over adjustment (results not shown)
Lederle et al. (2003)	• Prospective cohort (Cancer Prevention Study II) • 508,351 participants; >30 years of age; tended to be White, married, and educated; 1,296 deaths from AAA • Participants were screened between October 1992 and March 1995 • United States (all 50 states) • Follow-up: 14 years	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker: 2.4 – Current smoker: 6.0	Unpublished data presented in systematic review; 95% CIs not provided; adjusted for age and potentially other factors

Table 4.19 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Wong et al. (2007)[a]	• Prospective cohort (Health Professionals Follow-Up Study) • 39,352 men, 40–75 years of age at baseline, 10% current smokers at baseline, healthy (no prior CVD), excluded nondrinkers who had quit in prior 10 years, 376 cases of AAA • 1986–2002 • United States	• Smoking status: – Current smoker: 1.00 (referent) – Former smoker (years since quitting): ○ <10: 6.5 (4.5–9.3) ○ ≥10: 2.5 (1.8–9.3) – Current smoker (number of cigarettes smoked per day): ○ 1–4: 1.8 (0.4–7.4) ○ 5–14: 5.9 (3.0–11.4) ○ 15–24: 14.2 (9.4–21.5) ○ ≥25: 15.2 (9.9–23.3)	—
Forsdahl et al. (2009)[a]	• Prospective cohort study (Tromsø) • 4,345 participants, 25–82 years of age at baseline, 59.5 years of age (mean), 37% former smokers, no AAA or unknown AAA status, 119 incident cases of AAA • 1994–2001 • Norway	• Smoking status: – Never smoker: 1.00 (referent) – Former smoker (years since quitting): ○ <10: 2.88 (1.23–6.75) ○ 10–19: 2.90 (1.25–6.72) ○ ≥20: 1.26 (0.54–2.96) – Current smoker (number of cigarettes smoked per day): ○ <10: 6.19 (2.86–13.38) ○ 10–19: 9.78 (4.89–19.58) ○ ≥20: 13.72 (6.12–30.78)	Logistic regression used; cross-sectional analyses (Singh et al. 2001) found smoking was a risk factor for prevalence of AAA
Kent et al. (2010)[a]	• Cross-sectional analysis (prevalence in cohort, Life Line Screening database) • 3.1 million participants without prior repair of AAA, <85 years of age, 63.1 years of age (mean), 35% men, 87% White (also Hispanic, African American, Native American, and Asian), and 23,446 with AAA (≥3 cm) • Screened in 2003–2008 • United States	• Smoking status: – Current smoker: 1.00 (referent) – Former smoker (years since quitting): ○ <5: 0.87 (0.84–0.912) ○ 5–10: 0.68 (0.65–0.71) ○ >10: 0.42 (0.41–0.43)	

Table 4.19 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Pujades-Rodriguez et al. (2015)	• Prospective cohort • 1.93 million participants, ≥30 years of age, 49% men, predominantly White (also South Asian and Black), 16.2% former smokers (among those with smoking data); drawn from CALIBER program (linked electronic health records), no history of CVD, 1,238 cases of AAA in former smokers • 1997–2010 • England • Median follow-up: 6 years	• AAA by smoking status (age-adjusted): – Current smoker: 1.00 (referent) – Former smoker (years since quitting): ○ <2: 0.84 (0.47–1.51) ○ 2–9: 0.78 (0.52–1.17) ○ >10: 0.25 (0.20–0.32)	See Table 4.17 for concerns about validity
Stackelberg et al. (2014)[a]	• Two prospective cohorts (Cohort of Swedish Men and Swedish Mammography Cohort) • Participants 46–84 years of age, 37% of men were former smokers, 25% of women were former smokers, no known diagnosis of AAA or cancer (other than nonmelanoma skin cancer) • Sample sizes and number of AAAs by cohort: – Cohort of Swedish Men: 42,596, 958 AAA – Swedish Mammography Cohort: 35,550, 199 AAA • 1998–2011 • Sweden • Mean follow-up: 12.7 years	• Men: – Never smoker: 1.00 (referent) – Former smoker (<20 years since quitting): 3.77 (3.08–4.63) – Former smoker (≥20 years since quitting): 1.61 (1.27–2.03) – Current smoker (<20 pack-years): 3.06 (2.37–3.95) – Current smoker (≥20 pack-years): 6.55 (5.36–7.99) • Women: – Never smoker: 1.00 (referent) – Former smoker (<20 years since quitting): 4.63 (3.04–7.06) – Former smoker (≥20 years since quitting): 0.82 (0.35–1.92) – Current smoker (<20 pack-years): 7.01 (4.63–10.62) – Current smoker (≥20 pack-years): 6.55 (5.36–7.99)	Less power to detect associations in women (199 cases) than in men (958 cases)

Table 4.19 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Tang et al. (2016)[a]	• Prospective cohort (Atherosclerosis Risk in Communities Study) • 26% former smokers • 15,703 participants, 45–64 years of age at baseline, 45% men, 26% former smokers at baseline, African Americans (27%) and Whites, no prior repair of AAA, excluded uncertain AAA status during follow-up, 590 incident clinical AAAs, 5,578 participants underwent ultrasound screening from 2011 to 2013 (identified 75 asymptomatic AAAs) • 1987–2011 • United States • Median follow-up: 22.5 years	• Incident clinical AAAs: – Baseline smoking status: ○ Never smoker: 1.00 (referent) ○ Former smoker: 2.45 (1.85–3.25) ○ Current smoker: 7.59 (5.78–10.0) – Longitudinal smoking status: ○ Never smoker: 1.00 (referent) ○ Quit before first visit: 1.83 (1.19–2.81) ○ Recent quitter[b]: 3.50 (1.53–8.04) ○ Continuous smoker: 6.41 (3.67–11.2) • Similar pattern of associations with prevalent asymptomatic AAAs detected in 2011–2013 subgroup	—

Notes: **AAA =** abdominal aortic aneurysm; **CALIBER =** Clinical research using LInked Bespoke studies and Electronic health Records; **CI =** confidence interval; **cm =** centimeter; **RR =** risk ratio.

[a]Measure(s) of association adjusted for covariate(s).

[b]Recent quitter defined as someone who had quit for at least 3–8 years after the first visit in 1987.

time since smoking cessation (Table 4.19). Even so, in a comparison restricted to men and using never smokers as the referent, the age-adjusted hazard of AAA was still elevated in those who had quit smoking for 10 or more years (HR = 1.47, 95% CI, 1.10–1.95).

Prognosis of AAA

In the Aneurysm Detection and Management study, Bhak and colleagues (2015) assessed 534 veterans for the clinical risk factors associated with the expansion rate of AAA (i.e., the rate at which the AAA widens). The expansion rate of AAA is important to monitor, because (1) the risk of an AAA rupture is proportional to the maximum diameter of the AAA and (2) the mortality rate for rupture is high in those with aneurysms greater than 4–5 cm in diameter (Hirsch et al. 2006). Current smokers had an aortic expansion rate 0.05 cm/year greater (95% CI, 0.2–0.8) than former smokers—a 19% increase (Bhak et al. 2015).

Bhak and colleagues (2015) performed a pooled analysis of individual-level data from 12 studies. In one of the 12 studies, Sweeting and colleagues (2012) found that, compared with former and never smoking, current smoking increased the growth rate of AAA by 0.35 mm/year, and the rupture rate was twice as high in men and women who were current smokers as it was in nonsmokers. In another of the 12 studies (Brady et al. 2004), among 1,743 patients in the United Kingdom Small Aneurysm Trial, the growth rate of AAA was 0.42 mm/year higher in current smokers than in former smokers (95% CI, 0.17–0.68). There was no difference in the growth rate of AAA between former and never cigarette smokers. Using this same study population, Brown and Powell (1999) found that the adjusted hazard of AAA rupture was lower in former smokers (HR = 0.59; 95% CI, 0.39–0.89) than in current smokers. Other researchers have also found that smoking or a history of smoking is associated with an increased growth rate in AAA (Chang et al. 1997; Lindholt et al. 2001).

Koole and colleagues (2012) assessed the relationships between smoking status and outcomes of endovascular aneurysm repair among 8,638 patients (2,406 former smokers) in the European Collaborators on Stent/Graft Techniques for Aortic Aneurysm Repair study. Compared with never smokers, former and current smokers were more likely to need percutaneous transluminal angioplasty procedures or stents at the time of surgery (10.5%, 11.8%, and 13.7%, respectively). Regarding late complications, however, current smokers and former smokers had fewer endoleaks than never smokers. Current cigarette smokers (adjusted HR = 1.45; 95% CI, 1.03–2.05) and former smokers (adjusted HR = 1.23; 95% CI, 0.87–1.72) were more likely than never smokers to have migration of the stent graft.

Summary of the Evidence

Substantial evidence suggests that former smokers have a lower risk of incident AAA than current smokers and that risk decreases with increasing time since smoking cessation. Compared with never smokers, former smokers have an increased risk of AAA that can persist for decades. The evidence also suggests that the diameter of AAA expands at a lower rate in former smokers compared with current smokers.

Summary of the Evidence

This section builds on the 1990 (USDHHS 1990) and subsequent Surgeon General's reports (USDHHS 2001, 2004, 2006, 2010, 2014), providing an updated and overarching summary of what is now known about the relationships between smoking cessation and CVD outcomes. Previous Surgeon General's reports concluded that smoking cessation reduces the risk of CHD, PAD, ischemic stroke, SAH, and, more broadly, CVD morbidity and mortality (Table 4.10). These past reports also concluded that smoking cessation reduces risk of recurrent MI or CVD death among persons with CHD and improves exercise tolerance, reduces risk of amputation, and improves overall survival among patients with PAD. In particular, the 2001 Surgeon General's report concluded that smoking cessation appears to slow the rate of progression of carotid atherosclerosis in women and is associated with improvements in symptoms, prognosis, and survival among women with peripheral vascular atherosclerosis (USDHHS 2001). The evidence presented in this report shows that smoking cessation benefits persons at any age, reducing relative risk of CVD for smokers and the burden of disease from cardiovascular causes.

This section summarizes the large body of evidence related to the benefits of smoking cessation for reducing risk of CVD outcomes, considering evidence from mechanistic, epidemiologic, and clinical studies and applying established guidelines for causal inference (consistency; strength of association; temporality; specificity; experiment and biologic gradient; and coherence, plausibility, and analogy). Previous reports (U.S. Department of Health, Education, and Welfare [USDHEW] 1964; USDHHS 2004) have described this approach to causal inference. The approach is used here to systematically develop the basis for causal conclusions. As described in the 2004 Surgeon General's report, rather than serving as a checklist for assessing causal inference, these causal criteria are used to integrate multiple lines of evidence (USDHHS 2004).

Evaluation of the Evidence

Consistency

The relationships between smoking status and cessation with most of the outcomes described here have been extensively studied in well-designed and adequately powered studies (using observational and experimental designs) across different populations and time periods. Multiple studies have found that smoking cessation is associated with reduction in inflammatory markers and hypercoagulability and with rapid improvement in levels of HDL-C. Several, but not all, studies have found an association between smoking cessation and improved endothelial function. Much evidence documents the fact that former cigarette smokers tend to have less extensive subclinical atherosclerosis than current smokers and that smoking cessation is followed by slower progression of atherosclerosis, particularly for the outcomes of carotid IMT and ABI.

Many studies have also found that, compared with current smokers, former smokers have a lower risk of incident CVD, CHD, stroke, and AAA and that the risks decrease with increasing time since cessation. Studies support similar associations between smoking cessation and outcomes related to AF, SCD, heart failure, VTE, and PAD, although the evidence is more limited with regard to reduced risk with increased time since cessation. Additionally, smoking cessation is consistently associated with reduced risk of recurrent infarction and CVD death among patients with CHD (USDHHS 1990). Similarly, for persons who have already had a stroke, cessation reduces risk for recurrent events. Studies have also found that among patients with PAD, morbidity and mortality are lower in former smokers than in current smokers; in addition, the expansion rate of AAA is lower in former smokers than in current smokers.

Strength of Association

For many CVD outcomes, there is consistent evidence of a substantial reduction in risk among former smokers compared with current smokers; after a certain amount of time has elapsed since cessation, the risk for some outcomes among former smokers even approaches that of never smokers. For example, research estimates that the excess risk of CHD decreases by half approximately 4–5 years after cessation, albeit with substantial variation in estimates among studies, and then gradually approaches the risk of never smokers. For stroke, a similar pattern has been observed, although the risk may not reach that of never smokers. Smoking is strongly related to the risk of AAA; former smokers (particularly those who have quit for long periods) tend to have a substantially lower risk than those who continue to smoke. For example, in adjusted analyses in the ARIC study, compared with never smokers, current smokers had 6.41 times the risk of a clinical AAA (95% CI, 3.67–11.2); recent quitters (who had quit for at least 3–8 years) had 3.50 times the risk (95% CI, 1.53–8.04); and longer term quitters had 1.83 times the risk (95% CI, 1.19–2.81) (Tang et al. 2016).

Temporality

Many of the studies reviewed here are prospective in nature, and thus smoking status or smoking cessation was measured before the incident outcome. For measurements of biomarkers, several studies assessed changes in these biomarkers after cessation; similar analyses have been carried out for markers of subclinical atherosclerosis. Although some studies are cross-sectional in nature, prospective cohort studies have been carried out for each of the main outcomes discussed, thereby ensuring that smoking cessation preceded the occurrence of the health outcomes. The potential for reverse causality has also been accounted for in these studies to diminish the potential for such bias.

Specificity

In line with observations of reduced risk of overall CVD morbidity or mortality among former smokers compared with current smokers, similar reductions were observed for major causes of CVD morbidity and mortality, such as CHD and stroke and many other subtypes of CVD.

Experiment and Biologic Gradient

Both smoking cessation and time since cessation serve as naturally occurring changes in exposure status that can be used to infer the effect of the intervention of stopping smoking. The temporal pattern of declining risk after smoking cessation is strong evidence for a causal benefit of quitting and reflects a waning of the processes of injury caused by smoking. For most of the CVD outcomes reviewed in this report, most cited studies found a reduction in risk after cessation, followed by a pattern of a continued decrease in risk with longer time since cessation. In parallel, studies using biomarkers found greater reductions in inflammatory markers and hypercoagulability with increasing time since cessation. Evidence from observational studies and clinical trials supports a rapid (within weeks) improvement in levels of HDL-C after cessation, with no clear pattern of change after that time (Forey et al. 2013). Complementary evidence comes from studies showing greater reduction in risk with longer time since cessation for outcomes of incident CVD, congestive heart failure, stroke, and AAA. For the outcomes of incident AF, SCD, heart failure, VTE, and PAD, there

is less evidence available on how risk of these outcomes changes with time since cessation, although the available evidence supports a decrease in risk with increased time since cessation for SCD (Sandhu et al. 2012), heart failure (Pujades-Rodriguez et al. 2015), and PAD (Cui et al. 2006; Conen et al. 2011; Pujades-Rodriguez et al. 2015).

The 1990 Surgeon General's report estimated that excess risk of CHD is reduced by about half after 1 year of smoking cessation and that risk of CHD is similar among former and never smokers after 15 years of smoking cessation (USDHHS 1990). Similarly, the 2001 Surgeon General's report concluded that there is a substantial reduction in risk of CHD among women within 1–2 years of cessation; such a reduction in risk gradually continued to reach that of nonsmokers 10–15 or more years after cessation (USDHHS 2001). More recent analyses using an exponential distribution to quantitatively estimate how rapidly CHD risk decreases after smoking cessation indicate that the excess risk of CHD associated with smoking decreases by 50% about 4.4 years after cessation (95% CI, 3.26–5.95) (Lee et al. 2012). The risk then decreases asymptotically toward the risk among never smokers, as was also reported by the IARC (2007). Another model suggests a rapid decline in risk of acute MI soon after cessation, followed by a slower decline to a risk close to that of never smokers (Hurley 2005).

Similarly, the 1990 Surgeon General's report concluded that after smoking cessation, the risk of stroke returns to that of never smokers within 5–15 years (USDHHS 1990). The 2001 Surgeon General's report modified this conclusion slightly, stating that in most studies, including studies of women, the increased risk of stroke associated with smoking is reversible after cessation, with this risk approaching that of never smokers after 5–15 years of cessation. Another modeling study by Lee and colleagues (2014) estimated that the excess risk of stroke associated with smoking decreases by 50% after 4.78 years (95% CI, 2.17–10.50), but there was considerable unexplained heterogeneity. The modeling study by Hurley (2005) reported a rapid decrease in risk of stroke shortly after cessation (within 1–2 years), followed by a slower decline; the decline in risk of stroke was not as rapid as the decline in risk of acute MI following cessation, and the risk of stroke was estimated to remain elevated even among long-time former smokers. Evidence also supports a reduction in risk of mortality and of subsequent CVD events among patients with CHD who quit smoking after an index CHD event compared with those who continue to smoke (Wilson et al. 2000; Critchley and Capewell 2003; Twardella et al. 2004, 2006; Shah et al. 2010; Breitling et al. 2011a) (Table 4.20). Studies of the impact of counseling on smoking cessation have also found reduced risk of all-cause mortality among patients who received or were randomized to receive such counseling (Mohiuddin et al. 2007; Van Spall et al. 2007; Bucholz et al. 2017).

Coherence, Plausibility, and Analogy

Evidence linking smoking cessation to reduced risk of CVD should be considered within the broader context of mechanistic research on smoking and CVD. Previous reports concluded that smoking initiates several pathogenetic mechanisms that underlie the development of CVD (USDHHS 2004, 2010, 2014). The 1990 and 2001 Surgeon General's reports and the present updated review have provided evidence of how smoking cessation can reverse or slow these pathogenetic processes (USDHHS 1990) and slow the progression of subclinical atherosclerosis (USDHHS 2001).

Previous reports have also concluded that smoking causes CVD, including subclinical atherosclerosis, CHD, stroke, and AAA (USDHHS 2004). Much evidence supports a dose-response relationship between pack-years of smoking and risk of CVD. Evidence from the present report and previous reports supports the benefits of smoking cessation in terms of reducing risk of CVD. Multiple studies have found a larger relative benefit of cessation among those who quit smoking at younger ages (compared with those who quit later in life), which also aligns with research on the dose-response relationship between smoking and risk of CVD (Doll et al. 2004; Jha et al. 2013; Pirie et al. 2013; Thun et al. 2013a). However, given the increasing rates of the various CVDs with increasing age, substantial absolute reductions in the number of CVD events and deaths can still be made by quitting smoking at older ages.

Synthesis of the Evidence

The conclusions presented below are based on interpretations of multiple lines of evidence from a framework built around the guidelines for causal inference. Generally, when the evidence (a) is strong and consistent, (b) shows that former smokers have a lower risk of a CVD outcome (clinical or subclinical) compared with current smokers, (c) shows that the risk of a CVD outcome in former smokers decreases with increased time since cessation, and (d) results from well-designed and sufficiently powered studies, then such evidence is deemed sufficient to support the conclusion that smoking cessation causes a reduction in risk of the CVD outcome. When evidence for CVD outcomes is not as strong (e.g., if evidence on how CVD risk changes with time since cessation is not sufficient), then the evidence is deemed to be suggestive but not sufficient that smoking cessation decreases the risk of these outcomes.

Table 4.20 Observational studies (meta-analyses and individual cohorts) on smoking cessation and prognosis of coronary heart disease or cardiovascular disease

Study	Design/population	Findings: RR (95% CI)	Comments
Critchley and Capewell (2003)	• Meta-analysis of 20 prospective cohorts: – Total mortality analysis: n = 12,603; 2,928 cases – Nonfatal MI analysis: n = 6,089; 779 cases • Participants with prior CHD: – Mean: 55 years of age – 20% of cases were women (6 studies of men only) – 28–77% cessation rates (mean: 45%) • Most studies began in the 1960s or 1970s • Most from United States or Europe; one from Japan; and one from India • Follow-up: 2–26 years; mean: 5 years • Outcomes: total mortality and nonfatal MI	• Total mortality: – Continued smokers: 1.00 (referent) – Cessation group: 0.64 (0.58–0.71) • Nonfatal MI: – Continued smokers: 1.00 (referent) – Cessation group: 0.68 (0.57–0.82)	Restriction to high-quality studies yielded similar results; results were also similar across studies, irrespective of age, sex, index cardiac event, country, or year the study began
Dagenais et al. (2005)[a]	• Prospective analyses of clinical trial (Heart Outcomes Prevention Evaluation) • 8,905 participants with stable CVD or diabetes and one additional risk factor (approximately 50% had prior MI); 58% were former smokers • Cases (restricted to those who survived for 6 months): – CVD death: 641 – MI: 978 – Stroke: 358 – Total mortality: 1,021 • Started in 1993 • Median follow-up: 4.5 years	• Cardiovascular death, MI, or stroke: – Never smoker: 1.00 (referent) – Former smoker: 0.91 (0.80–1.03) – Current smoker: 1.37 (1.14–1.64) – Similar findings for individual outcomes of CVD death, MI, and stroke • Mortality: – Never smoker: 1.00 (referent) – Former smoker: 0.93 (0.80–1.08) – Current smoker: 1.99 (1.63–2.44) • No consistent pattern for increased risk of heart failure, revascularization, unstable angina, or occurrence of microalbuminuria	—

Table 4.20 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Breitling et al. (2011a)[a]	• Prospective cohort study (Long-Term Success of Cardiologic Rehabilitation Therapy study) • 1,062 participants: – Mean: 59 years of age – 85% male with acute MI, coronary syndrome, or coronary artery intervention seen for rehabilitation – 154 cases who had secondary CVD events • Started in 2000 • Germany • Median follow-up: 8.1 years • Outcome: secondary CVD events	• Abstained from smoking according to self-report: – Continued smoker: 1.00 (referent) – Quit after event: 0.38 (0.20–0.73) – Quit before event: 0.62 (0.40–0.97) – Never smoker: 0.47 (0.28–0.78) • Restricted to those who did not change status for 1–3 years: – Continued smoker: 1.00 (referent) – Quit after event: 0.17 (0.06–0.44) – Quit before event: 0.42 (0.25–0.70) – Never smoker: 0.32 (0.18–0.55)	Similar findings for 1-year and 3-year follow-ups (Twardella et al. 2004, 2006)

Notes: **CHD =** coronary heart disease; **CI =** confidence interval; **CVD =** cardiovascular disease; **MI =** myocardial infarction; **RR =** risk ratio.
[a]Measure(s) of association adjusted for covariate(s).

Conclusions

1. The evidence is sufficient to infer that smoking cessation reduces levels of markers of inflammation and hypercoagulability and leads to rapid improvement in the level of high-density lipoprotein cholesterol.

2. The evidence is sufficient to infer that smoking cessation leads to a reduction in the development of subclinical atherosclerosis, and that progression slows as time since cessation lengthens.

3. The evidence is sufficient to infer that smoking cessation reduces the risk of cardiovascular morbidity and mortality and the burden of disease from cardiovascular disease.

4. The evidence is sufficient to infer that the relative risk of coronary heart disease among former smokers compared with never smokers falls rapidly after cessation and then declines more slowly.

5. The evidence is sufficient to infer that smoking cessation reduces the risk of stroke morbidity and mortality.

6. The evidence is sufficient to infer that, after smoking cessation, the risk of stroke approaches that of never smokers.

7. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of atrial fibrillation.

8. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of sudden cardiac death among persons without coronary heart disease.

9. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of heart failure among former smokers compared with persons who continue to smoke.

10. Among patients with left-ventricular dysfunction, the evidence is suggestive but not sufficient to infer that smoking cessation leads to increased survival and reduced risk of hospitalization for heart failure.

11. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of venous thromboembolism.

12. The evidence is suggestive but not sufficient to infer that smoking cessation substantially reduces the risk of peripheral arterial disease among former smokers compared with persons who continue to smoke, and that this reduction appears to increase with time since cessation.

13. The evidence is suggestive but not sufficient to infer that, among patients with peripheral arterial disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival.

14. The evidence is sufficient to infer that smoking cessation substantially reduces the risk of abdominal aortic aneurysm in former smokers compared with persons who continue to smoke, and that this reduction increases with time since cessation.

15. The evidence is suggestive but not sufficient to infer that smoking cessation slows the expansion rate of abdominal aortic aneurysm.

Implications

The evidence is clear and certain that smoking cessation reduces the risk for major CVD outcomes. The decline over time in the prevalence of adult cigarette smoking has contributed to the decline of CVD mortality. Intensified efforts by clinicians, healthcare systems, communities, and states to encourage and help smokers to quit will contribute to reducing the burden of CVD at the patient and population levels.

Smoking Cessation After a Diagnosis of Coronary Heart Disease

Heart disease is the leading cause of death in the United States for both men and women (Xu et al. 2018). The term "heart disease" refers to several types of heart conditions. In the United States the most common type of heart disease is coronary artery disease, which affects the blood flow to the heart. Smoking is a key risk factor for developing coronary heart disease (CHD) (U.S. Department of Health and Human Services [USDHHS] 2004).

This section reviews the evidence on the benefits of cigarette smoking cessation in people with established

CHD. It focuses on the endpoints of all-cause mortality, cause-specific mortality, and the incidence of new or recurrent cardiac events. As advances in clinical treatment regimens for CHD have improved the prognosis for persons with cardiovascular events, the previously established evidence that smoking represents a causal factor for CHD has led to studies investigating the potential benefit of smoking cessation for reducing risk of mortality after a diagnosis. The body of evidence on this topic, which began to emerge in the 1970s, has grown to the point that substantial scientific evidence now exists on this topic.

Conclusions from Previous Surgeon General's Reports

Previous Surgeon General's reports have not specifically evaluated the evidence concerning the impact of cigarette smoking cessation on mortality after a diagnosis of CHD; in fact, this is the first Surgeon General's report to address the potential health benefits of smoking cessation after such a diagnosis. Previous reports have concluded that sufficient evidence exists to infer that smoking causes premature death, multiple diseases, and other adverse health effects (USDHHS 2014). The 1990 report, which focused on the benefits of smoking cessation, reported conclusions on the decline in risk for CHD and stroke among those who quit smoking compared with those who continued to smoke. In addition, the report concluded that, "Among persons with diagnosed CHD, smoking cessation markedly reduces the risk of recurrent infarction and cardiovascular death. In many studies this reduction in risk of recurrence or premature death has been 50 percent or more" (USDHHS 1990, p. 260). The report noted a lack of relevant findings for stroke.

Considering the biological processes by which smoking increases risk for multiple diseases and mortality, the adverse health effects of smoking would be expected to apply to persons diagnosed with CHD in the same way as they apply to persons in the general population who are at risk for first events. The 2010 Surgeon General's report, *How Tobacco Smoke Causes Disease,* detailed the many mechanisms leading to these adverse health effects (USDHHS 2010).

Biological Basis

This review emphasizes all-cause mortality, cause-specific mortality, and the incidence of new or recurrent cardiac events. Regarding all-cause mortality, the mortality burden from smoking is largely attributable to its role in causing multiple types of cancer, various cardiovascular diseases, and chronic obstructive pulmonary disease (COPD). Many aspects of the pathogenesis of these diseases in smokers have been characterized, and these same mechanisms would apply to persons who have been diagnosed with CHD (USDHHS 2010). With regard to the risk for cardiovascular disease following cessation, the risk for several consequences of smoking—including endothelial dysfunction, increased risk for thrombosis, and reduced oxygen delivery—would be expected to lessen in the short term after cessation (USDHHS 2010). As detailed in the 2014 Surgeon General's report, in addition to causally increasing risk for specific disease endpoints, smoking causes systemic inflammation and oxidative stress and has widespread and complex effects on immune function (USDHHS 2014). The 2004 Surgeon General's report concluded that smoking causes overall poorer health that leaves smokers with a diminished health status compared with nonsmokers (USDHHS 2004).

Literature Review Methods and Other Methodologic Considerations

The literature search strategy for this review was designed to have high sensitivity by searching broadly in the MEDLINE database and then manually identifying articles with evidence on the association between smoking cessation in patients with CHD and clinical endpoints. For example, key terms in the initial search included "smoking cessation" and "coronary heart disease" OR "cardiovascular disease." The relevant evidence identified was most abundant on the specific topics of the associations between persistent smoking versus quitting smoking with the outcomes of all-cause mortality, cause-specific mortality (focused on cardiac causes of death and sudden death), and risk of new or recurrent cardiac events. Consequently, the evidence review for this section focuses on these three endpoints.

Because of the methodologic limitations of other designs, the summary tables in this section include data only from original research reports on prospective cohort studies. Relevant systematic reviews and meta-analyses were incorporated into the discussion of the evidence, but they were not included in the evidence tables. The reference lists of all published papers reviewed, including the systematic reviews, were searched to check for potentially eligible studies.

Several points relevant to considerations of methodology were consistent across the range of outcomes addressed. First, because all evidence summarized in the evidence tables was generated from prospective cohort

studies, it benefited from the methodologic strengths of such studies in addressing the question of the effect of smoking cessation in patients with CHD. Specifically, these were studies of cohorts of patients diagnosed with a specific heart disease, most often myocardial infarction (MI), or who had undergone a specific cardiovascular procedure such as percutaneous coronary intervention (PCI) or coronary bypass surgery. In all the studies, smoking status was measured at the time of initial diagnosis. To assess the health effects of smoking cessation, areas of interest included findings only from those who were current smokers at the time of diagnosis; this review did not consider results pertaining to those who were never smokers or former smokers at diagnosis. Further, a follow-up measurement of smoking status after baseline was required to distinguish those who quit smoking (henceforth called "quitters") from those who remained smokers (henceforth called "persistent smokers"). The timing of the follow-up assessment of smoking status represents a key study design feature because only patients who survived to the follow-up assessment were eligible for inclusion in the cohorts, as explained below. The more remote the follow-up assessment from the start of follow-up, the greater the likelihood for cohort attrition due to mortality; to the extent that persistent smokers experience greater mortality soon after the cardiac diagnosis, there would be an increasing bias toward the null with a lengthening interval from baseline to follow-up.

The definitions of "quitters" and "persistent smokers" varied across studies, ranging from sustained abstinence or continued smoking across several longitudinal follow-up points to self-reported quitting or continued smoking at a single follow-up time point. Alternatively, in some studies smoking status was analyzed as a time-dependent variable to account for the many possible transitions in smoking status that can take place over time. After the baseline assessment, current smokers could be classified as quitters or persistent smokers on the basis of a follow-up assessment; at that point, the prospective follow-up for outcomes began. With these shared features of study design, this body of evidence is focused specifically on those who were current smokers at the time of the cardiac diagnosis, with the analysis targeting the effect of quitting compared with persistent smoking within this population. Of note, several studies were initially randomized treatment trials in which sufficient data had been collected to address smoking cessation within the context of a subsequent observational cohort study of trial participants.

For the endpoint of all-cause mortality, evidence tables (Tables 4.21 and 4.22) present details of 34 reports from 32 studies. The index diagnosis used to define the patient cohorts was MI (or included MI with other conditions such as angina) in the majority (61%) of studies on this topic. Other index diseases were coronary artery disease (CAD) (15% of studies); CHD (6% of studies); and in one study, cardiac arrest. Among studies that defined the cohort on the basis of an index procedure, the most common procedures were PCI (9% of studies) and coronary artery bypass surgery (6%). The studies included in the evidence tables for cause-specific mortality (Table 4.23) and new/recurrent cardiac events (Table 4.24) numbered 13 and 15, respectively.

Epidemiologic and Clinical Evidence

Smoking Cessation and All-Cause Mortality in Patients with Coronary Heart Disease

Table 4.21 summarizes studies (N = 24) of cohorts of patients who were current smokers at the time of a CHD diagnosis that assessed the association between smoking cessation and all-cause mortality by comparing quitters and persistent smokers (the referent). Although all the studies relied on prospective cohorts, they varied widely in sample size, population composition, duration of follow-up, and consideration of potential confounding variables. Sample sizes ranged from 87 to 8,489 persons, and follow-up ranged from 6 months to 30 years. Some estimates of relative risk (RR) were unadjusted, and others were extensively adjusted for demographic, lifestyle, family history, or clinical characteristics. Despite this variability in design features, the results across studies were consistent, as illustrated by the forest plot in the top portion of Figure 4.4. When quitters were compared with persistent smokers, this forest plot, which illustrates results for the 24 studies that included an RR estimate and 95% confidence interval (CI) for all-cause mortality, shows that the RR estimates in every case were less than 1.0. The estimates ranged from 0.11 to 0.93, with a median RR of 0.55, or a reduction of 45% in the rate of mortality. The study showing the weakest association (Chow et al. 2010) (RR = 0.93; 95% CI, 0.59–1.46) also had the shortest follow-up (6 months); this may be too brief a period to observe the full impact of quitting (versus persistent smoking) on mortality. When the results of this study were presented on the basis of a composite outcome of MI or stroke or death, the results aligned more closely with those of other studies (RR = 0.74; 95% CI, 0.53–1.02) (Chow et al. 2010).

One of the 24 studies (Breitling et al. 2011a) in Table 4.21 measured self-reported smoking and also incorporated a biomarker of smoking (blood concentration of cotinine). This study found that smoking classification based on self-reports alone underestimated the strength of

Table 4.21 Summary of results from prospective cohort studies of patients with coronary heart disease who were cigarette smokers at diagnosis, comparing all-cause mortality in those who quit smoking with persistent cigarette smokers

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Wilhelmsson et al. (1975)	• 405 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3 months after MI • 231 quitters, 174 persistent smokers • Study period: 1968–1972 • Sweden • 2-year follow-up results presented	• 0.51 (0.27–0.96)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated on basis of data presented in Table 5 in Wilhelmsson and colleagues (1975)
Sparrow and Dawber (1978)	• Framingham Study • 195 patients with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as former smokers or persistent smokers based on smoking status after • data collection immediately preceding and following MI (indeterminate timing) • 56 quitters, 139 persistent smokers • Cohort established 1949, 22 years of follow-up through 1978 • United States • 6-year follow-up results presented	• 0.62 (0.33–1.15)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated on basis of data presented on page 429 in Sparrow and Dawber (1978)
Baughman et al. (1982)	• 87 patients with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after infarct (indeterminate timing) • 45 quitters, 42 persistent smokers • Enrollment period: 1968–1971, with follow-up through 1978 • United States • 99-month mean follow-up (survivors)	• 0.35 (0.18–0.66)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated on basis of data presented at top of right-hand column on page 877 in Baughman and colleagues (1982)

Table 4.21 Continued

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Mulcahy et al (1982)	• 517 male patients <60 years of age with first diagnosis of unstable angina or MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters if stopped smoking at least 3 months before last follow-up or death (indeterminate timing) • 282 quitters, 235 persistent smokers • Enrollment period: 1961–1975 with follow-up through 1979 • Ireland • 99-month mean follow-up (survivors)	• 0.59 (0.47–0.73)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated on basis of data presented in Table 1 in Mulcahy and colleagues (1982)
Aberg et al. (1983)	• 983 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3-month follow-up • 542 quitters, 441 persistent smokers • Enrollment period: 1968–1977 • Sweden • 10.5 years maximum follow-up	• All-cause mortality: – All ages: 0.63 (0.50–0.79) – ≤50 years of age: 0.46 (0.25–0.84) – >50 years of age: 0.65 (0.50–0.83) • 5-year survival: – Quitters: 84% – Persistent smokers: 78% – p <0.0001	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Presented survival plots and p values only from Cox proportional hazards regression models Risk ratio calculated from data presented in Table 6 in Aberg and colleagues (1983)
Perkins and Dick (1985)	• 119 patients with first-time diagnosis of MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI (indeterminate timing) • 52 quitters, 67 persistent smokers • Enrollment period: 1974–1977 • United Kingdom • 5-year follow-up	• 0.39 (0.20–0.74)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated from data presented in Table II in Perkins and Dick (1985)

Table 4.21 Continued

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Rønnevik et al. (1985)	• 453 patients with first-time diagnosis of AMI who were current smokers at diagnosis within a randomized controlled trial • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI on basis of continued follow-up (indeterminate timing) • 276 quitters, 177 persistent smokers • Enrollment period: 1978–1979 • Norway • Mean follow-up: 17.3 months	• All-cause mortality (placebo group): 0.74 (0.42–1.30)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Results presented limited to placebo group because of observed interaction of treatment (timolol) with smoking Risk ratio calculated from data presented in Table 3 in Rønnevik and colleagues (1985)
Hallstrom et al. (1986)	• 310 patients with cardiac arrest who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status 2 months or less after cardiac arrest • 91 quitters, 219 persistent smokers • Study period: 1970–1981 • United States • Mean follow-up: 47.5 months	• 0.79 (0.50–1.06)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated from data presented in bottom right-hand column of page 272 of Hallstrom and colleagues (1986)
Burr et al. (1992)	• DART • 1,186 nondiabetic male patients ≤70 years • of age with MI who were current smokers at diagnosis and survived at least 6 months • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 665 quitters, 521 persistent smokers • Study period: indeterminate • United Kingdom • 18-month follow-up	• 0.52 (0.32–0.83)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Mortality ratios based on average annual mortality rates Unadjusted risk ratio calculated from Table 2 in Burr and colleagues (1992)

Table 4.21 Continued

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Cavender et al. (1992)	• CASS • 284 patients with angiographically confirmed CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 97 quitters, 187 persistent smokers • Enrollment period: 1974–1979 • United States and Canada (15 clinical sites) • 10-year follow-up	• All-cause mortality: 0.63 (0.40–0.97) • 10-year survival: – Quitters: 80% – Persistent smokers: 69% – p = 0.025	Quitters vs. persistent smokers (referent) Unadjusted risk ratios "Persistent smoker" defined as a person who smoked during the follow-up interval (questionnaires every 6 months) Risk ratio calculated from data presented in the title of Figure 2 in Cavender and colleagues (1992); a Cox proportional hazards model was fit with smoking as a time-dependent covariate to account for quitters who reverted to smoking Cox proportional hazards model showed that smoking during 50% and 100% of the follow-up period increased the RR of death by 1.56 and 1.73, respectively Survival plots and p values presented only from Cox proportional hazards regression models
Gupta et al. (1993)	• 225 patients with CHD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status since the time of diagnosis of CAD (indeterminate timing) • 173 quitters, 52 persistent smokers • Study baseline: 1980 • India • Approximately 6-year follow-up	• 0.70 (0.49–1.01)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated from data presented on page 127 of Gupta and colleagues (1993) Adjusted hazards ratio comparing persistent smokers to quitters plus nonsmokers presented in Table 3 in Gupta and colleagues (1993) underestimated association because of inclusion of nonsmokers in the reference category; hazard ratio was 1.28 (95% CI, 1.01–2.09) after adjusting for sex, age, hypertension, cholesterol, diabetes, and history of MI or congestive heart failure

Table 4.21 Continued

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Tofler et al. (1993)	• MILIS study • 641 patients with AMI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 360 quitters, 281 persistent smokers • Enrollment period: 1974–1979 • United States • 4-year follow-up results presented	• All-cause mortality: – Total: 0.48 (0.31–0.73) – <12 years of education: 0.63 (0.39–1.03) – ≥12 years of education: 0.39 (0.18–0.89)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated from data presented in Table 3 in Tofler and colleagues (1993)
Greenwood et al. (1995)	• ASSET • 532 patients with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1-month follow-up • 396 quitters, 136 persistent smokers • Study period: 1986–1988 (enrollment) • England • 6.3-year median follow-up	• All-cause mortality: 0.56 (0.33–0.98) • 10-year survival: – Quitters: 80% – Persistent smokers: 69% – p = 0.025	Quitters vs. persistent smokers (referent) Logistic regression models Adjusted for age, history of diabetes, history of angina, and treatment with antiarrhythmic drugs at discharge
Herlitz et al. (1995)	• 217 patients with AMI who were current smokers at diagnosis and survived at least 1 year • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after 1 year of follow-up • 115 quitters, 102 persistent smokers • Enrollment period: 1986–1987 • Sweden • 4-year follow-up results presented	• 0.55 (0.34–0.91)	Quitters vs. persistent smokers (referent) Unadjusted risk ratios Risk ratio calculated on basis of data presented in text and mortality rates presented in Figure 2 in Herlitz and colleagues (1995)

Table 4.21 Continued

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Kinjo et al. (2005)	• OACIS study • 1,424 patients with AMI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status 3 months after discharge • 1,056 quitters, 368 persistent smokers • Study period: 1998–2003 • Japan • 2.5-year mean follow-up	• Adjusted hazard ratio: 0.39 (0.20–0.77)	Quitters vs. persistent smokers (referent) Proposed hazards models Adjusted for sex, age, BMI, hypertension, dyslipidemia, diabetes, obesity, prior MI, prior angina pectoris, prior cerebrovascular disease, heart rate, Killip class ≥2, anterior wall MI, atrial fibrillation, ventricular fibrillation, and revascularization
Gerber et al. (2009)	• ISFAMI • 798 patients ≤65 years of age with first-time MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up • 417 quitters, 381 persistent smokers • Study period: 1992–2005 • Israel • 13.2-year median follow-up	• Adjusted odds ratio: 0.63 (0.48–0.82)	Quitters vs. persistent smokers (referent) Proportional hazards models, with smoking modeled as time-dependent covariate Adjusted for sex, age, ethnicity, education, income, employment, hypertension, dyslipidemia, diabetes, obesity, physical activity, Q-wave AMI, CABG, PTCA, unstable angina pectoris, and heart failure during follow-up
Chow et al. (2010)	• OASIS 5 trial • 4,324 patients with unstable angina or MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after 30 days of follow-up • 2,802 quitters, 1,522 persistent smokers • Study baseline: 2003–2005 • 41 countries • 6-month follow-up	• Adjusted odds ratio: 0.93 (0.59–1.46)	Quitters vs. persistent smokers (referent) Logistic regression models Paper presented measures of association as odds ratios, but because they were from a prospective cohort study, these are RR estimates Adjusted for sex, age, hypertension history, diabetes, prior MI, BMI, creatinine, PCI/CABG before 30 days, and medications

Table 4.21 Continued

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Shah et al. (2010)	• SAVE trial • 731 patients with AMI with left ventricular systolic dysfunction who were current smokers at diagnosis • All current smokers at baseline who survived at least 6 months • Categorized as quitters or persistent smokers based on smoking status after 6 months of follow-up • 463 quitters, 268 persistent smokers • Study baseline: 1987–1990 • United States • 42-month median follow-up	• Adjusted hazard ratio for all-cause mortality by follow-up interval: – 6 months: 0.57 (0.36–0.91) – 12 months: 0.58 (0.33–0.99) – 16 months: 0.60 (0.34–1.07) – 24 months: 0.53 (0.25–1.08)	Quitters vs. persistent smokers (referent) Proportional hazards regression models Propensity score (on basis of 24 parameters) adjusted model Reduction in risk started early and was maintained over time Results presented combined mortality with MI or hospitalization for heart failure
Breitling et al. (2011a)	• KAROLA study • 1,062 total patients with AMI, coronary syndrome, coronary artery intervention who were current smokers at diagnosis • All results presented in table limited to current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at rehabilitation discharge • Numbers of quitters and persistent smokers vary by classification method • 85% men, mean 59 years of age • Study baseline: 2000 • Germany • 8.1-year median follow-up	• Outcome was fatal or nonfatal secondary cardiovascular disease events (MI, ischemic stroke, deaths with cardiovascular disease as the main cause): – Self-report plus cotinine (169 quitters, 154 persistent smokers): adjusted hazard ratio 0.38 (0.20–0.73) – Self-report plus cotinine, limited to those who remained quitters or persistent smokers throughout follow-up (101 quitters, 98 persistent smokers): adjusted hazard ratio 0.17 (0.06–0.44) – Self-report only (204 quitters, 53 persistent smokers): adjusted hazard ratio 0.75 (0.35–1.60)	Hazard ratio for quitters vs. persistent smokers Results indicate that using a biomarker of smoking results in greater magnitude of risk reduction compared with self-report alone Results indicate that magnitude of risk reduction is greater when maintaining abstinence Taken in combination, these findings indicate that the association with quitting smoking is likely underestimated in most studies because studies of this type typically have not used biomarkers and continuous maintenance of smoking abstinence Earlier results from this same study showing similar findings were included in Twardella and colleagues (2006) Adjusted for sex, age, diabetes, triglycerides, total and LDL cholesterol, and ACE inhibitor at discharge

Table 4.21 Continued

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Chen et al. (2012)	• 8,489 patients undergoing PCI (stent implantation) who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up (indeterminate timing) • 4,440 quitters, 4,049 persistent smokers • Study period: 2004–2010 • China • 3.0-year median follow-up	• Adjusted hazard ratio: 0.11 (0.06–0.22)	Hazard ratio for quitters vs. persistent smokers Adjusted for sex, age, diabetes, prior MI, hypertension, hyperlipidemia, prior bypass surgery, unstable angina, family history of CHD, ejection fraction, lesion type, reference vessel diameter, lesion length, restenotic lesion, calcification, angulated/total occlusion, thrombus, predilation, stent length, and postdilation
Álvarez et al. (2013)	• FRENA registry • 1,182 patients who were current smokers at diagnosis • 475 with CAD, 240 with CVD, 467 with PAD • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 512 quitters, 670 persistent smokers • Study period: 2003–2010 • Spain • 14-month mean follow-up	• Adjusted hazard ratio: 0.51 (0.22–1.15)	Mortality ratio for quitters vs. persistent smokers Adjusted for comorbidity, atrial fibrillation, medications, and creatinine clearance
de Boer et al. (2013)	• 497 patients undergoing PCI who were current smokers at diagnosis and survived at least 1 year • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1-year follow-up • 210 quitters, 287 persistent smokers • Study baseline: 1980–1985 • Netherlands • 19.5-year median follow-up, 30 years maximum • 56 years of age average	• All cause-mortality: adjusted hazard ratio 0.57 (0.46–0.71) • 30-year survival: 2.1 times as high in quitters as in persistent smokers (29% vs. 14%) • Life expectancy: 2.1 years longer in quitters vs. persistent smokers (18.5 vs. 16.4 years)	Adjusted hazard ratio comparing quitters plus nonsmokers vs. persistent smokers Having the baseline age of the cohort combined with a 30-year follow-up period enabled unique evaluation of impact on survival; adjustments not clearly specified, but there appears to have been adjustment for sex, age, indication for PCI, diabetes, prior MI, hypertension, hyperlipidemia, prior bypass surgery, multivessel disease, clinical success of PCI, and family history of CHD

Table 4.21 Continued

Study	Design/population	Findings: RR[a] (95% CI)	Comments
Liu et al. (2013)	• 430 male CHD patients undergoing PCI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status immediately after the index procedure (indeterminate) • 283 quitters, 147 persistent smokers • Study baseline: 2009–2010, follow-up to 2012 • China • Follow-up 27.2 months (assumed to be average)	• Risk ratio: 0.17 (0.05–0.63)	Risk ratio calculated from data presented in Table 2 in Liu and colleagues (2013); data represent major clinical outcomes for persistent smokers, quitters, and nonsmokers Adjusted hazard ratio comparing persistent smokers to quitters plus nonsmokers presented in Table 3 in Liu and colleagues (2013) will underestimate association because of inclusion f nonsmokers in the reference group; hazard ratio was 2.43 (95% CI, 1.17–5.05) after adjusting for age, hypertension, dyslipidemia, aspirin use, and statin use
Hammal et al. (2014)	• APPROACH registry • 2,583 patients undergoing coronary angiography for CAD who were current smokers at diagnosis and survived at least 1 year • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1-year follow-up • 1,519 quitters, 1,064 persistent smokers • Study period: 2003–2010 • Canada • 42.2-month mean follow-up • 56 years of age (mean)	• Outcome all-cause mortality plus comparison of survival: – Total cohort (unmatched): 0.54 (0.39–0.73) – Subgroup receiving medical treatment (matched): 0.59 (0.31–1.11) – Subgroup receiving revascularization: 0.46 (0.22–0.96) – Survival in total cohort: 95.7% in quitters vs. 92.0% in persistent smokers – Survival in subgroup receiving medical treatment: 93.0% in quitters vs. 88.0% in persistent smokers – Survival in subgroup receiving revascularization: 94.9% in quitters vs. 88.9% in persistent smokers (p <0.05)	Quitters vs. persistent smokers Risk ratios calculated from data presented in Table 7 in Hammal and colleagues (2014) No explicit adjustments; matching was on basis of propensity scores

Notes: **ACE =** angiotensin-converting enzyme; **AMI =** acute myocardial infarction; **APPROACH =** Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease; **ASSET =** Anglo-Scandinavian Study of Early Thrombolysis; **BMI =** body mass index; **CABG =** coronary artery bypass grafting; **CAD =** coronary artery disease; **CASS =** Coronary Artery Surgery Study; **CHD =** coronary heart disease; **CI =** confidence interval; **DART =** Diet and Reinfarction Trial; **FRENA =** Factores de Riesgo y ENfermedad Arterial [Registry]; **ISFAMI =** Israel Study of First Acute Myocardial Infarction; **KAROLA =** Langzeiterfolge der Kardiologischen Anschlussheilbehandlung (Long-Term Success of Cardiologic Rehabilitation Therapy); **LDL =** low-density lipoprotein; **MI =** myocardial infarction; **MILIS =** Multicenter Investigation of Limitation of Infarct Size; **OACIS =** Osaka Acute Coronary Insufficiency Study; **OASIS =** Organization to Assess Strategies in Acute Ischemic Syndromes; **PAD =** peripheral artery disease; **PCI =** percutaneous coronary intervention; **PTCA =** percutaneous transluminal coronary angioplasty; **RR =** relative risk; **SAVE =** Sleep Apnea Cardiovascular Endpoints.
[a]RR unless specified otherwise.

Table 4.22 Summary of results from prospective cohort studies of patients with coronary heart disease who were cigarette smokers at diagnosis, comparing all-cause mortality in those who remained persistent smokers with those who quit smoking

Study	Design/population	Findings: RR (95% CI)	Comments
Salonen (1980)	• 523 male patients ≤65 years of age with MI • who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 221 quitters, 302 persistent smokers • Enrollment period: 1968–1977 • Finland • 3-year follow-up	• 1.7 (1.1–2.6)	Persistent smokers vs. quitters (referent) Unadjusted rate ratios
Daly et al. (1983)	• 374 patients with unstable angina or MI • who were current smokers at diagnosis and survived at least 2 years • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 2-year follow-up • 217 quitters, 157 persistent smokers • Enrollment period: 1974–1979 • Ireland • 7.4-year mean follow-up, 13-year follow-up after smoking status defined	• 2.8 (p <0.01)	Persistent smokers vs. quitters (referent) Mortality ratios calculated from average annual mortality rates Unadjusted rate ratios Presented survival plots and p values only from Cox proportional hazards regression models
Johansson et al. (1985)	• 156 female patients with MI who were current smokers at diagnosis and survived at least • 3 months • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3 months of follow-up • 81 quitters, 75 persistent smokers • Study period: 1968–1977 • Ireland • 7.4-year mean follow-up, 13-year follow-up after smoking status defined	• Unadjusted: 2.3 (1.2–4.4) • Fully adjusted: 2.7 (CI not presented)	Persistent smokers vs. quitters (referent) Unadjusted rate ratios Cox proportional hazards models; fully adjusted model included mean peak SAST, Q waves, and angina pectoris known before the infarction Presented survival plots Example of adjustment resulting in stronger association

Table 4.22 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Vliestra et al. (1986)	• CASS • 4,165 patients with angiographically confirmed CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at time of diagnosis • 1,490 quitters, 2,675 persistent smokers • Enrollment period: 1975–1977 • United States (15 clinical sites) • 5-year follow-up results presented	• 1.55 (1.29–1.85)	Persistent smokers vs. quitters (referent) Quitters had a worse prognostic profile than persistent smokers at baseline The definition of persistent smoker was self-reported smoking at every follow-up The definition of quitter was someone who quit 1 year before study entry and reported not smoking at every follow-up Cox proportional hazards models using a propensity-score approach to adjust for covariates Propensity-score adjustment approach on basis of the following variables: age, sex congestive heart failure score, left ventricular wall motion score, CAGE 50, surgery, left ventricular end-diastolic blood pressure, hypertension, diabetes, Gensini score, prior MI, degree of functional impairment because of congestive heart failure, left main coronary stenosis of ≥50%
Hermanson et al. (1988)	• CASS • 1,893 patients with CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters based on quitting smoking within 1 year before the baseline angiogram • 807 quitters, 1,086 persistent smokers • Enrollment period: 1974–1979 • United States • Average follow-up: 5.3 years	• All-cause mortality, total: 1.7 (1.4–2.0) • All-cause mortality stratified by age group (years): – 55–64: 1.7 (1.4–2.1) – ≥70: 1.6 (1.1–2.3) – 55–59: 1.5 (1.1–2.0) – 60–64: 2.0 (1.5–2.6) – 65–69: 1.4 (0.9–2.0) – ≥70: 3.3 (1.5–7.1)	Persistent smokers vs. quitters (referent) Hazard ratios Same CASS as in Vliestra and colleagues (1986) Presented age-specific associations

Table 4.22 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Peters et al. (1995)	• CAST I and CAST II • 1,026 patients with left ventricular dysfunction after MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 517 quitters, 509 persistent smokers • Enrollment period: 1987–1991 • United States • 15.5-month mean follow-up	• 1.64 (0.97–2.79)	Persistent smokers vs. quitters (referent) Cox proportional hazards regression models using smoking as a time-dependent covariate Adjusted for sex, age, angina, heart failure, ejection fraction, history of MI, diabetes, hypertension, history of coronary artery angioplasty or bypass grafts, history of diabetes, history of congestive heart failure, CAST treatment condition, angina, use of thrombolytic agents during qualifying MI, and other study-specific treatment variables
Voors et al. (1996)	• 167 patients with coronary bypass surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1 year of follow-up • 72 quitters, 95 persistent smokers • Enrollment period: 1976–1977 • Netherlands • 15 years of follow-u	• 0.9 (0.5–1.6)	Persistent smokers vs. quitters (referent) Cox proportional hazards regression models This result is for the complete follow-up period from 1 year to 15 years after surgery In Table 6 in Voors and colleagues (1996), the result for 5 to 15 years after surgery was an RR of 1.7 (95% CI, 0.8–3.5) adjusted for sex, age, plus the following variables if p <0.10 (unclear from text which variables met this criterion): obesity; elevated cholesterol and triglyceride levels; angina; heart failure; ejection fraction; history of MI, diabetes, and/or hypertension; family history of CAD, diabetes, and/or congestive heart failure; and number of vessels diseased and other characteristics of index diagnosis
Hasdai et al. (1997)	• 1,169 patients who had undergone successful percutaneous coronary revascularization who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up • 435 quitters, 734 persistent smokers • Study period: 1979–1995 • United States • 4.5-year mean follow-up, 16-year maximum	• 1.44 (1.02–2.11)	Persistent smokers vs. quitters (referent) Proportional hazards models Adjusted for significant differences in baseline variables Unclear which variables were included in the model, but baseline variables included sex, age, angina, heart failure, ejection fraction, diabetes, hypertension, and family history of CAD

Table 4.22 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
van Domburg et al. (2000)	• 556 patients who had undergone CABG surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status >1 year after CABG (median 2.8 years) • 238 quitters, 318 persistent smokers • Study period: 1971–1980 • Netherlands • 20-years median follow-up (range 13–26 years)	• 1.68 (1.33–2.13)	Persistent smokers vs. quitters (referent) Proportional hazards models Adjusted for sex, age, vessel disease, ejection fraction, and complete revascularization
Zhang et al. (2015)	• SYNTAX • 1,793 patients with complex CAD who were current smokers at diagnosis • Use of time-dependent covariates may have included all participants (never, former, and current smokers at baseline) • Smoking categorized at 6 months, 1 year, 3 years, and 5 years of follow-up • Indeterminate study period • Multicenter, multinational study • 5 years of follow-up	• 1.80 (1.27–2.54)	Smoking status analyzed as a time-dependent covariate Cox proportional hazards regression models Composite endpoint of death/MI/stroke Never precisely specified, but this estimate likely included the total study population, including never smokers and former smokers as well as current smokers at baseline Assume adjusted for other independent predictors listed in Table 3 in Zhang and colleagues (2015): PCI vs. CABG, age, COPD, PVD, LVEF <30%, amiodarone therapy on discharge (never specified in text)

Notes: **CABG =** coronary artery bypass grafting; **CAD =** coronary artery disease; **CAGE 50 =** number of segments with coronary artery stenosis ≥50%; **CASS =** Coronary Artery Surgery Study; **CAST =** Cardiac Arrhythmia Suppression Trial; **CI =** confidence interval; **COPD =** chronic obstructive pulmonary disease; **LVEF =** left ventricular ejection fraction; **MI =** myocardial infarction; **PVD =** peripheral vascular disease; **PCI =** percutaneous coronary intervention; **RR =** relative risk; **SAST =** serum aspartate amino transferase; **SYNTAX =** SYNergy between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery Trial.

Table 4.23 Summary of results from prospective cohort studies of patients with coronary heart disease who were cigarette smokers at diagnosis, comparing cause-specific mortality from cardiac endpoints and sudden death in those who remained persistent cigarette smokers with those who quit smoking

Study	Design/population	Findings: RR (95% CI)	Comments
Wilhelmsson et al. (1975)	• 405 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3 months following MI • 231 quitters, 174 persistent smokers • Study period: 1968–1972 • Sweden • 2-year follow-up results presented	• Cardiovascular death: 2.05 (0.99–4.27)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated using the data presented in Table 5 in Wilhelmsson and colleagues (1975)
Salonen (1980)	• 523 male patients ≤65 years of age with MI • who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 6-month follow-up • 221 quitters, 302 persistent smokers • Enrollment period: 1968–1977 • Finland • 3-year follow-up	• Ischemic heart disease: 1.6 (1.0–2.7) • Other cardiovascular disease: 1.5 (0.3–8.0)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios
Mulcahy et al. (1982)	• 517 male patients <60 years of age with first diagnosis of unstable angina or MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters based on stopping smoking at least 3 months before the last follow-up or death (indeterminate timing) • 282 quitters, 235 persistent smokers • Enrollment period: 1961–1975, with follow-up through 1979 • Ireland • 99-month mean follow-up (survivors)	• Cardiac failure: 2.70 (0.84–8.66) • Sudden death: 1.77 (1.23–2.54) • Fatal MI: 1.68 (1.04–2.72)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated using data presented in Table 2 in Mulcahy and colleagues (1982)

Table 4.23 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Daly et al. (1983)	• 374 patients with unstable angina or MI • who were current smokers at diagnosis and survived at least 2 years • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 2-year follow-up • 217 quitters, 157 persistent smokers • Enrollment period: 1974–1979 • Ireland • 7.4-year mean follow-up, 13-year follow-up after smoking status defined	• Vascular causes: 2.4 ($p < 0.01$) • Fatal reinfarction: 2.6 ($p = 0.02$) • Sudden death: 1.6 ($p = 0.14$)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Mortality ratios based on average annual mortality rates Presented survival plots and p values only from Cox proportional hazards regression models
Rønnevik et al. (1985)	• 453 patients with first-time diagnosis of acute MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI with continued follow-up (indeterminate time) • 276 quitters, 177 persistent smokers • Enrollment period: 1978–1979 • Norway • Mean follow-up 17.3 months	• Cardiac causes (placebo group): 1.17 (0.62–2.22)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated from data presented in Table 3 in Rønnevik and colleagues (1985) Results presented limited to the placebo group because of an observed interaction of the treatment (timolol) with smoking
Hallstrom et al. (1986)	• 310 patients with cardiac arrest who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status 2 months or less after cardiac arrest • 91 quitters, 219 persistent smokers • Study period: 1970–1981 • United States • Mean follow-up 47.5 months	• Cardiac arrest: 1.55 (0.98–2.45)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated from data presented on page 272 in Hallstrom and colleagues (1986)

Table 4.23 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Vliestra et al. (1986)	• CASS Trial • 4,165 patients with angiographically confirmed coronary artery disease who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at time of diagnosis • 1,490 quitters, 2,675 persistent smokers • Enrollment period: 1975–1977 • United States (15 clinical sites) • 5-year follow-up results presented	• Cardiac contributing: 1.60 (0.89–2.86) • Sudden death: 1.82 (1.14–2.89) • MI: 1.78 (1.36–2.33)	Persistent smokers vs. quitters (referent) Cox proportional hazards models using a propensity score approach to adjust for covariates Quitters had a worse prognostic profile than persistent smokers at baseline The definition of persistent smoker was self-reported smoking at every follow-up; the definition of a quitter was someone who had quit 1 year before study entry and reported not smoking at every follow-up Propensity-score adjustment approach based on age, sex, congestive heart failure score, left ventricular wall motion score, CAGE 50, surgery, left ventricular end-diastolic blood pressure, hypertension, diabetes, Gensini score, prior MI, degree of functional impairment because of congestive heart failure, left main coronary stenosis of ≥50%
Hermanson et al. (1988)	• CASS • 1,893 patients with CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters based on quitting smoking within 1 year before the baseline angiogram • 807 quitters, 1,086 persistent smokers • Study period: 1974–1979 (enrollment) • United States • Average follow-up 5.3 years	• Cardiac causes: 1.37 (p = .001)	Persistent smokers vs. quitters (referent) Hazard ratios Overall and stratified by age group Same CASS as in Vliestra et al. (1986) Risk ratio calculated from data presented on page 1,367 of Hermanson and colleagues (1988)

Table 4.23 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Gupta et al. (1993)	• 225 patients with CHD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status since the time of diagnosis of CAD (indeterminate) • 173 quitters, 52 persistent smokers • Study baseline: 1980 • India • ~ 6-year average follow-up	• Sudden death: 1.48 (0.81–2.71)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated from data presented on page 127 of Gupta and colleagues (1993)
Peters et al. (1995)	• CAST I and CAST II • 1,026 patients with left ventricular dysfunction after MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 517 quitters, 509 persistent smokers • Enrollment period: 1987–1991 • United States • 15.5-month mean follow-up	• Arrhythmic mortality: 1.80 (0.88–3.67)	Persistent smokers vs. quitters (referent) Cox proportional hazards regression models using smoking as a time-dependent covariate Adjusted for sex, age, angina, heart failure, ejection fraction, history of MI, diabetes, hypertension, history of coronary artery angioplasty or bypass grafts, history of diabetes, history of congestive heart failure, CAST treatment condition, angina, use of thrombolytic agents during qualifying MI, and other study-specific treatment variables
Hasdai et al. (1997)	• 1,169 patients who had undergone successful percutaneous coronary revascularization who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up • 435 quitters, 734 persistent smokers • Study period: 1979–1995 • United States • 4.5-year mean follow-up, 16 years maximum	• Cardiac causes: 1.49 (0.89–2.51)	Persistent smokers vs. quitters (referent) Proportional hazards models Adjusted for significant differences in baseline variables Unclear which variables were included in the model, but baseline variables included sex, age, angina, heart failure, ejection fraction, diabetes, hypertension, and family history of CAD

Table 4.23 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
van Domburg et al. (2000)	• 556 patients who had undergone CABG surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status >1 year after CABG (median 2.8 years) • 238 quitters, 318 persistent smokers • Study period: 1971–1980 • Netherlands • 20-year median follow-up (range 13–26 years)	• Cardiac causes: 1.75 (1.30–2.37)	Persistent smokers vs. quitters (referent) Proportional hazards models Adjusted for sex, age, vessel disease, ejection fraction, and complete revascularization
Liu et al. (2013)	• 430 male CHD patients undergoing • percutaneous coronary intervention who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status immediately after the index procedure (indeterminate) • 283 quitters, 147 persistent smokers • Study baseline: 2009–2010, follow-up to 2012 • China • Follow-up 27.2 months (assumed to be average)	• Cardiac causes: 7.7 (0.9–68.8)	Persistent smokers vs. quitters (referent) Risk ratio calculated from data presented in Table 2 in Liu and colleagues (2013)

Notes: **CABG =** coronary artery bypass grafting; **CAD =** coronary artery disease; **CAGE 50 =** number of segments with coronary artery stenosis ≥50%; **CASS =** Coronary Artery Surgery Study; **CAST =** Cardiac Arrhythmia Suppression Trial; **CHD =** coronary heart disease; **CI =** confidence interval; **MI =** myocardial infarction; **RR =** relative risk.

Table 4.24 Summary of results from prospective cohort studies of patients with coronary heart disease who were cigarette smokers at diagnosis, comparing incidence of cardiac endpoints in those who remained persistent cigarette smokers with those who quit smoking or vice versa

Study	Design/population	Findings: RR (95% CI)	Comments
Wilhelmsson et al. (1975)	• 405 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3 months following MI • 231 quitters, 174 persistent smokers • Study period: 1968–1972 • Sweden • 2-year follow-up results presented	• Reinfarction: 0.49 (0.29–0.82)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated based on the data presented in Table 5 in Wilhelmsson and colleagues (1975)
Sparrow and Dawber (1978)	• Framingham Study • 195 patients with MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after data collection immediately preceding and following MI (indeterminate timing) • 56 quitters, 139 persistent smokers • Cohort established 1949: 22 years of follow-up through 1978 • United States • 6-year follow-up results presented	• Reinfarction: 0.76 (0.37–1.58)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated based on data presented on page 430 in Sparrow and Dawber (1978)
Aberg et al. (1983)	• 983 male patients with first MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 3-month follow-up • 542 quitters, 441 persistent smokers • Enrollment period: 1968–1977 • Sweden • 10.5-year maximum follow-up	• Reinfarction: 0.67 (0.53–0.84)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated from data presented in Table 7 in Aberg and colleagues (1983)

Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Perkins and Dick (1985)	• 119 patients with first-time diagnosis of MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI (indeterminate time) • 52 quitters, 67 persistent smokers • Enrollment period: 1974–1977 • United Kingdom • 5-year follow-up	• Reinfarction: 3.87 (0.81–18.37)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated from data presented in Table II in Perkins and Dick (1985)
Rønnevik et al. (1985)	• 453 patients with first-time diagnosis of acute MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after MI based on continued follow-up (indeterminate time) • 276 quitters, 177 persistent smokers • Enrollment period: 1978–1979 • Norway • Mean follow-up 17.3 months	• MI: 0.54 (0.32–0.93)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Results presented limited to the placebo group because of an observed interaction of treatment (timolol) with smoking Risk ratio calculated from data presented in Table 3 in Rønnevik and colleagues (1985)

Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Vliestra et al. (1986)	• CASS • 4,165 patients with angiographically confirmed CAD who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at time of diagnosis • 1,490 quitters, 2,675 persistent smokers • Enrollment period: 1975–1977 • United States (15 clinical sites) • 5-year follow-up results presented	• 5-year MI hospitalization: 0.63 (0.51–0.78)	Persistent smokers vs. quitters (referent) Cox proportional hazards models using a propensity score approach to adjust for covariates Propensity-score adjustment approach on basis of the following variables: age, sex, congestive heart failure score, left ventricular wall motion score, CAGE 50, surgery, left ventricular end-diastolic blood pressure, hypertension, diabetes, Gensini score, prior MI, degree of functional impairment because of congestive heart failure, left main coronary stenosis of ≥50% Quitters had a worse prognostic profile than persistent smokers at baseline The definition of persistent smoker was self-reported smoking at every follow-up; the definition of a quitter was someone who had quit 1 year before study entry and reported not smoking at every follow-up
Herlitz et al. (1995)	• 217 patients with acute MI who were current smokers at diagnosis and survived at least • 1 year • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after 1 year of follow-up • 115 quitters, 102 persistent smokers • Enrollment period: 1986–1987 • Sweden • 4-year follow-up results presented	• Reinfarction: 0.99 (0.42–2.33)	Persistent smokers vs. quitters (referent) Unadjusted risk ratios Risk ratio calculated from data presented in Table 4 in Herlitz and colleagues (1995)

Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
Voors et al. (1996)	• 167 patients with coronary bypass surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 1 year of follow-up • 72 quitters, 95 persistent smokers • Enrollment period: 1976–1977 • Netherlands • 15 years of follow-up	• MI: 2.3 (1.1–5.1) • Reoperation: 2.5 (1.1–5.9) • Angina: – 1–15 years post-surgery: 1.2 (0.8–1.7) – 5–15 years post-surgery: 2.0 (1.1–3.6	Persistent smokers vs. quitters (referent) Cox proportional hazards regression models Adjusted for sex, age, plus the following variables if p <0.10 (unclear from text which variables met this criterion): obesity, diabetes, elevated cholesterol and triglyceride levels, hypertension, history of heart failure, preoperative angina pectoris, family history of CAD, number of vessels diseased, completeness of revascularization, number of distal anastomoses, left ventricular function, history of MI, indication for operation, presence of collateral arteries, left main CAD, and proximal left anterior descending artery disease
Hasdai et al. (1997)	• 1,169 patients who had undergone successful percutaneous coronary revascularization who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up • 435 quitters, 734 persistent smokers • Study period: 1979–1995 • United States • 4.5-year mean follow-up, 16 years maximum	• MI: 0.68 (.54–.86)	Quitters vs. persistent smokers (referent) Proportional hazards model Never smokers were used as the referent for estimating the RRs; 0.68 was the RR of MI for quitters vs. never smokers, and 1.44 (1.02–2.11) was the RR for death for persistent smokers vs. never smokers Adjusted for significant differences in baseline variables Unclear which variables were included in the model, but baseline variables included sex, age, angina, heart failure, ejection fraction, diabetes, hypertension, and family history of CAD

Table 4.24 Continued

Study	Design/population	Findings: RR (95% CI)	Comments
van Domburg et al. (2000)	• 556 patients who had undergone CABG surgery who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status >1 year after CABG (median 2.8 years) • 238 quitters, 318 persistent smokers • Study period: 1971–1980 • Netherlands • 20-year median follow-up (range 13–26 years)	• Repeat CABG/PTCA: 1.41 (1.02–1.94)	Persistent smokers vs. quitters (referent) Proportional hazards models Adjusted for sex, age, vessel disease, ejection fraction, and complete revascularization
Chow et al. (2010)	• OASIS trial • 4,324 patients with unstable angina or MI who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status after 30 days of follow-up • 2,802 quitters, 1,522 persistent smokers • Study baseline: 2003–2005 • 41 countries • 6-month follow-up	• MI: 0.57 (0.36–0.89) • Stroke: 0.40 (0.14–1.17)	Quitters vs. persistent smokers (referent) Logistic regression models Paper presented measures of association as odds ratios, but for this prospective cohort study, these were converted to RR Adjusted for sex, age, hypertension history, diabetes, prior MI, BMI, creatinine, PCI/CABG before 30 days, and medications
Chen et al. (2012)	• 8,489 patients undergoing PCI (stent implantation) who were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status during follow-up (indeterminate timing) • 4,440 quitters, 4,049 persistent smokers • Study period: 2004–2010 • China • 3.0-year median follow-up	• Repeat revascularization: 1.59 (1.36–1.85)	Hazard ratio for quitters vs. persistent smokers Adjusted for sex, age, diabetes, prior MI, hypertension, hyperlipidemia, prior bypass surgery, unstable angina, family history of CHD, ejection fraction, lesion type, reference vessel diameter, lesion length, restenotic lesion, calcification, angulated/total occlusion, thrombus, predilation, stent length, and postdilation

Table 4.24 Continued

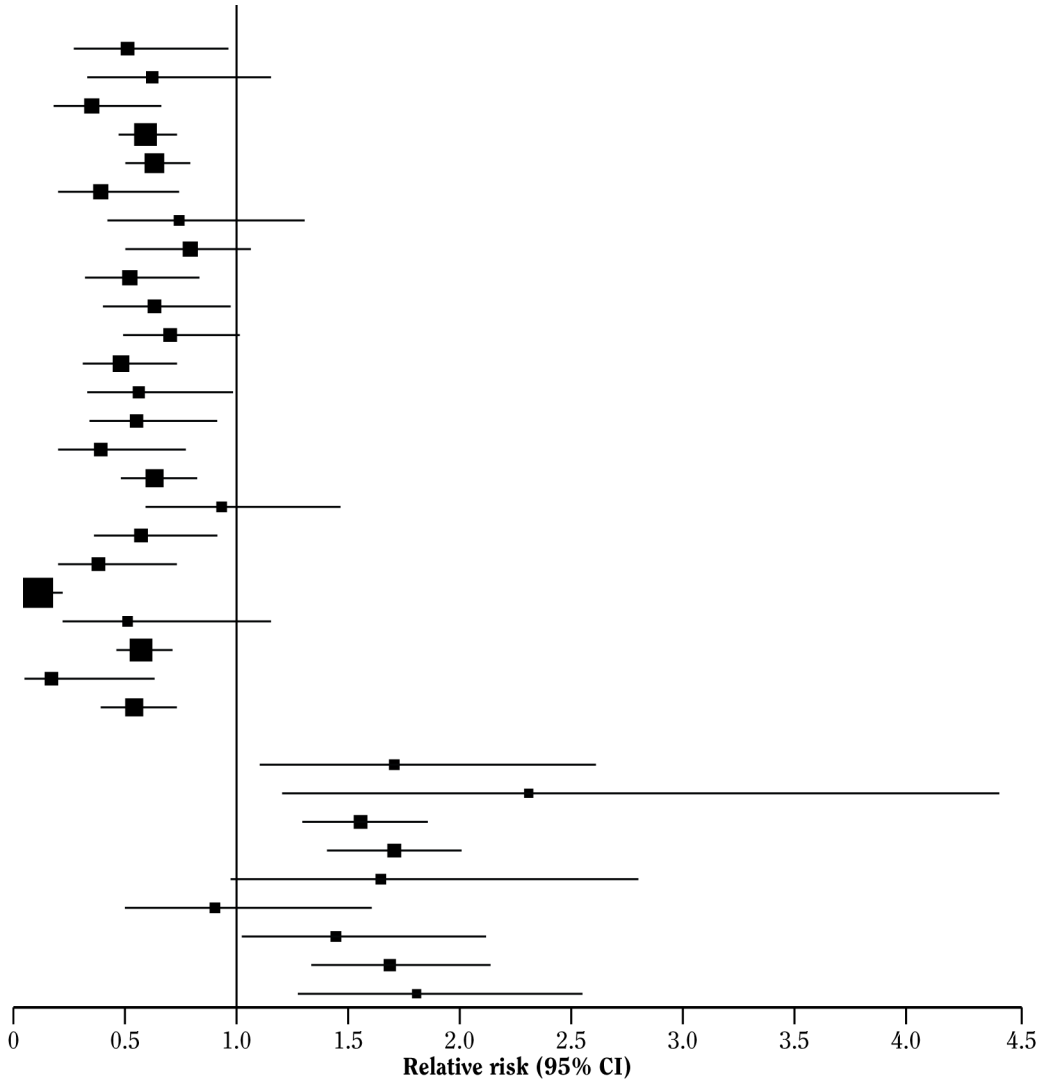
Study	Design/population	Findings: RR (95% CI)	Comments
Álvarez et al. (2013)	• FRENA registry • 1,182 patients who were current smokers at diagnosis • 475 with CAD, 240 with CVD, 467 with PAD • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 512 quitters, 670 persistent smokers • Study period: 2003–2010 • Spain • 14-month mean follow-up	• MI: 0.70 (0.26–1.88)	Mortality ratio for quitters vs. persistent smokers Adjusted for comorbidity, atrial fibrillation, medications, and creatinine clearance
Choi et al. (2013)	• Prospective cohort • 275 patients who were current smokers at diagnosis of MI • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status at 4-month follow-up • 144 quitters, 131 persistent smokers • Study period: 1999–2008 • South Korea • Regularly followed for 1 year after MI	• Re-intervention or MI: 2.9 (0.2–33.0)	Persistent smokers vs. quitters (referent) Risk ratio for re-intervention or MI Not clear that the estimate was adjusted for any factors
Liu et al. (2013)	• 430 male CHD patients undergoing PCI who • were current smokers at diagnosis • All current smokers at baseline • Categorized as quitters or persistent smokers based on smoking status immediately after the index procedure (indeterminate) • 283 quitters, 147 persistent smokers • Study baseline: 2009–2010, follow-up to 2012 • China • Follow-up 27.2 months (assumed to be average)	• Revascularization: 2.89 (1.05–8.0) • MI: – 1.4% in persistent smokers – 0% in quitters • RR for quitters vs. persistent = 0.0	Persistent smokers vs. quitters (referent) Risk ratio calculated from data presented in Table 2 in Liu and colleagues (2013) Adjusted hazard ratio comparing persistent smokers to quitters plus nonsmokers presented in Table 3 in Liu and colleagues (2013) will underestimate association because of inclusion of nonsmokers in the referent Hazard ratio was 2.43 (95% CI, 1.17–5.05) after adjusting for age, hypertension, dyslipidemia, aspirin use, and statin use

Notes: **BMI =** body mass index; **CABG =** coronary artery bypass grafting; **CAD =** coronary artery disease; **CAGE 50 =** number of segments with coronary artery stenosis ≥50%; **CASS =** Coronary Artery Surgery Study; **CHD =** coronary heart disease; **CI =** confidence interval; **CVD =** cardiovascular disease; **FRENA =** Factores de Riesgo y ENfermedad Arterial [Registry]; **MI =** myocardial infarction; **OASIS =** Organization to Assess Strategies in Ischemic Syndromes; **PAD =** peripheral artery disease; **PCI =** percutaneous coronary intervention; **PTCA =** percutaneous transluminal coronary angioplasty; **RR =** relative risk.

Figure 4.4 Relative risk for all-cause mortality after cardiac event among those who were current smokers when diagnosed, by smoking status

Study	Relative risk (95% CI)
Quit vs. persistent	
Wilhemsson et al. 1975	0.51 (0.27–0.96)
Sparrow et al. 1978	0.62 (0.33–1.15)
Baughman et al. 1982	0.35 (0.18–0.66)
Mulcahy et al. 1982	0.59 (0.47–0.73)
Aberg et al. 1983	0.63 (0.50–0.79)
Perkins et al. 1985	0.39 (0.20–0.74)
Rønnevik et al. 1985	0.74 (0.42–1.30)
Hallstrom et al. 1986	0.79 (0.50–1.06)
Burr et al. 1992	0.52 (0.32–0.83)
Cavender et al. 1992	0.63 (0.40–0.97)
Gupta et al. 1993	0.70 (0.49–1.01)
Tofler et al. 1993	0.48 (0.31–0.73)
Greenwood et al. 1995	0.56 (0.33–0.98)
Herlitz et al. 1995	0.55 (0.34–0.91)
Kinjo et al. 2005	0.39 (0.20–0.77)
Gerber et al. 2009	0.63 (0.48–0.82)
Chow et al. 2010	0.93 (0.59–1.46)
Shah et al. 2010	0.57 (0.36–0.91)
Breitling et al. 2011	0.38 (0.20–0.73)
Chen et al. 2012	0.11 (0.06–0.22)
Álvarez et al. 2013	0.51 (0.22–1.15)
de Boer et al. 2013	0.57 (0.46–0.71)
Liu et al. 2013	0.17 (0.05–0.63)
Hammal et al. 2014	0.54 (0.39–0.73)
Persistent vs. quit	
Salonen et al. 1980	1.70 (1.10–2.60)
Johansson et al. 1985	2.30 (1.20–4.40)
Vliestra et al. 1986	1.55 (1.29–1.85)
Hermanson et al. 1988	1.70 (1.40–2.00)
Peters et al. 1995	1.64 (0.97–2.79)
Voors et al. 1996	0.90 (0.50–1.60)
Hasdai et al. 1997	1.44 (1.02–2.11)
van Domburg et al. 2000	1.68 (1.33–2.13)
Zhang et al. 2015	1.80 (1.27–2.54)

Note: **CI =** confidence interval.



the association between cessation and mortality compared with classification of smoking by both self-reported and biomarker data. These results replicated previous findings from this research group (Twardella et al. 2006). Because most findings are based on self-reported smoking status, the pattern of associations in comparisons of self-reported with biomarker-based classification suggests that the associations observed in studies that rely on self-reported smoking may be underestimated because of the misclassification from self-reports.

Table 4.22 summarizes studies in cohorts of patients with CHD that assessed the association between smoking cessation and all-cause mortality by comparing persistent smokers with quitters as the reference group; the lower portion of Figure 4.4 presents a forest plot for the nine reports that included an RR and a 95% CI. Among the 10 reports from the 9 studies detailed in Table 4.22, all but 1 report showed an RR estimate of 1.44 or greater for persistent smokers. As can be seen in the forest plot, seven of the nine RR estimates it contains were statistically significant. The median RR was 1.67, indicative of an increase of two-thirds in the all-cause mortality rate in persistent smokers compared with quitters.

Taken together, the results of the studies summarized in Tables 4.21 and 4.22 and in Figure 4.4 show very clear, consistent, and strong associations. In total, 97% (31/32) of the studies reported associations indicating that smoking cessation was associated with a reduction in all-cause mortality when compared with persistent smoking. These associations were statistically significant in 78% (25/32) of the studies—a high proportion, given that 25% (8/32) of the studies had total samples of fewer than 300 patients and the median follow-up period was only 4.5 years. These results align closely with the results of meta-analyses published in 1999 (van Berkel et al. 1999) and in 2003 (Critchley and Capewell 2003) that reported summary RRs in quitters versus persistent smokers of 0.62 (95% CI, 0.57–0.68) (van Berkel et al. 1999) and 0.64 (95% CI, 0.58–0.71) (Critchley and Capewell 2003), respectively. When these associations are viewed from the reverse perspective of comparing persistent smokers with quitters, they are of a magnitude similar to the association of smoking with all-cause mortality in general cohorts, as reported in the 2014 Surgeon General's report (USDHHS 2014).

A central issue in assessing this body of evidence is that among current cigarette smokers diagnosed with CHD, those who quit may differ from persistent smokers in ways that could generate an apparent benefit of smoking cessation that reflects confounding. Many of the associations presented in the evidence tables in the present report are not adjusted for any potential confounding variables. The results in Table 4.21 that begin with the study of Kinjo and colleagues (2005) and then go up through a 2014 report were estimated mainly with Cox proportional hazard models that adjusted for a wide range of potential confounding variables. These 10 studies had RR estimates that ranged from 0.11 to 0.93, with a median of 0.52. Only 3 of the 17 RR estimates were 0.63 or higher, and the 3 lowest RRs equaled 0.11 (once) and 0.17 (twice), with those results indicating a very strong protective effect for quitting. Notably, the studies that compared the characteristics of quitters with persistent smokers found that quitters tended to be older and to have a predominance of other characteristics associated with a worse prognosis. This pattern could lead to confounding that would diminish a true association.

The presence of confounding is supported by the increased association observed in some studies that adjusted for potential confounding variables. For example, in the study by Johansson and colleagues (1985), which compared persistent smokers with quitters, the unadjusted RR of death was 2.3 for the persistent smokers, and after adjustment for the key prognostic factors that differed between persistent smokers and quitters, the RR increased to 2.7 (Table 4.22). Thus, confounding appears an unlikely explanation for the finding of reduced all-cause mortality in quitters versus persistent smokers among those who were current smokers at the time of diagnosis with a cardiac condition. In contrast, it could be helpful in explaining the results of studies in which quitters, not persistent smokers, were the referent.

Concerns about confounding can be further addressed by analyzing evidence from studies of smoking cessation interventions that provide evidence to address this issue. For example, in an observational cohort study of 13,815 patients diagnosed with MI who were current smokers discharged alive from the hospital, those who received an inpatient smoking cessation intervention were compared with those who did not receive this intervention (Bucholz et al. 2017). At 30 days of follow-up, those who received the intervention had significantly reduced all-cause mortality (hazard ratio [HR] = 0.77; 95% CI, 0.62–0.96), and this benefit persisted even after 17 years of follow-up (HR = 0.93; 95% CI, 0.89–0.96) after adjustment for a wide range of potential confounding variables.

Elsewhere, in a randomized controlled trial of an intensive smoking cessation intervention (n = 109) compared with usual care (n = 100) in a population of 30- to 75-year-olds diagnosed with acute cardiovascular disease, after 2 years of follow-up the intervention group had 4.3 times the proportion of continuous abstinence from smoking compared with the usual-care group (Mohiuddin et al. 2007). During this same 2-year interval, compared with the usual-care group, the intervention group experienced a 44% reduction in hospitalizations (RR = 0.56;

95% CI, 0.37–0.85) and a reduction of more than three-quarters in all-cause mortality (RR = 0.23; 95% CI, 0.07–0.79) (Mohiuddin et al. 2007). Given the randomized trial design, this study provides experimental evidence of the association between smoking cessation and reduced fatal and nonfatal outcomes. Associations of this magnitude from a high-quality experimental study with relatively short-term follow-up provide strong evidence supporting an immediate and direct benefit of quitting and greatly reduce the likelihood that uncontrolled confounding explains the results of the observational studies.

Smoking Cessation and Cause-Specific Mortality in Cardiac Patients

The indication of a strong inverse association between smoking cessation and all-cause mortality after patients are diagnosed with CHD raises a question as to which causes of death are affected. Table 4.23 presents 20 specific associations comparing persistent smokers to quitters from 13 studies of cohorts of patients with CHD that assessed smoking cessation in relation to cause-specific mortality; these studies focused on either specific cardiac endpoints or sudden death. The 16 RR estimates with CIs are summarized in forest plots in Figure 4.5.

The results shown in Figure 4.5 are stratified by cause-of-death groups, with "cardiac" and "cardiac contributing" comprising the largest group (n = 9 data points), followed by sudden death (n = 3 data points), fatal reinfarction (n = 2 data points), and 1 each for ischemic heart disease and arrhythmic mortality. The visual impression of consistently strong associations shown in Figure 4.5 is reinforced by the complete evidence in Table 4.23, as all 20 associations presented in the table indicate increased risk associated with persistent smoking, with RRs ranging from 1.17 to 7.70, with a median of 1.60. The RRs were statistically significant in 45% (9/20), a smaller proportion than observed for all-cause mortality; because the magnitudes of the RRs were similar for all-cause and cause-specific mortality, the reduced statistical precision due to the smaller numbers of deaths for cause-specific compared with all-cause mortality likely explains the lower proportion of significant estimates. This body of evidence demonstrates that in current smokers diagnosed with CHD, the reduction in all-cause mortality associated with smoking cessation is attributable, at least in part, to a reduction in mortality from cardiac outcomes and sudden death. Cigarette smoking is an established cause of MI and other cardiovascular endpoints, as reviewed in prior Surgeon General's reports (USDHHS 1983, 2010, 2014); thus, the associations reviewed in Table 4.23 and summarized in a forest plot in Figure 4.5 are consistent with prior evidence on this topic in the general population.

Smoking Cessation and Risk of Recurrence or New Cardiac Events in Cardiac Patients

Studies in cohorts of patients with CHD who were current smokers at the time of diagnosis that assessed the risk of new or recurrent cardiac events in relation to quitting versus persistent smoking are summarized in Table 4.24 and, for those studies with RRs and 95% CIs, in forest plots in Figure 4.6. Thirteen studies provided results for MI, including the outcomes of "reinfarction" and "MI hospitalization"; consistent with Figure 4.6, the associations tended to be either strongly in the protective direction for quitters compared with persistent smokers as the reference category (85% [11/13] RRs ≤0.76; overall median RR = 0.67) or, alternatively, strongly in the direction of increased risk for persistent smokers relative to quitters as the referent. Of the two studies with results not strongly in the protective direction, the associations were null in one (RR = 0.99; 95% CI, 0.42–2.33) (Herlitz et al. 1995) and positive in the other (RR = 3.87; 95% CI, 0.81–18.37) (Perkins and Dick 1985). As seen in Figure 4.6, these two studies introduce heterogeneity. The overall results of these studies comprise a strong body of evidence indicating that smoking cessation after a diagnosis of a previous MI or other cardiac disease reduces the risk of MI.

The results for the endpoints of stroke, angina, or repeat procedures also indicate benefit from smoking cessation—that is, reduced risk in quitters versus persistent smokers. One study found that quitters had a lower risk of stroke (RR = 0.40; 95% CI, 0.14–1.17) compared with persistent smokers, but the results were not statistically significant (Chow et al. 2010). The one study of angina (Voors et al. 1996) found a weak, nonsignificant association for the entire follow-up period (RR = 1.2; 95% CI, 0.8–1.7), but a significant association for the period from 5 to 15 years after surgery (RR = 2.0; 95% CI, 1.3–3.6). Four studies reported results using repeat procedures as endpoints; these included repeat coronary artery bypass grafting/percutaneous transluminal coronary angioplasty (CABG/PTCA), reoperation, and repeat vascularization. Three studies observed increased risk for repeat procedures—CABG/PTCA, reoperation, or repeat vascularization—in persistent smokers when quitters were the referent (RR ≥1.4). In the fourth study, authored by Chen and colleagues (2012), the results were strongly in the opposite direction, with an RR of 1.59 (95% CI, 1.36–1.85) for repeat revascularization in quitters compared with persistent smokers as the referent. This discrepant result notwithstanding, the overall evidence summarized in Table 4.24 and Figure 4.6 indicates reduced risk associated with smoking cessation relative to persistent smoking for the occurrence of adverse cardiac events among patients with CHD who were current smokers at diagnosis.

Figure 4.5 Cause-specific mortality from cardiovascular endpoints and sudden death in persistent smokers versus quitters

Study	Relative risk (95% CI)
Cardiac	
Wilhemsson et al. 1975	2.05 (0.99–4.27)
Salonen et al. 1980	1.50 (0.30–8.00)
Mulcahy et al. 1982	2.70 (0.84–8.66)
Rønnevik et al. 1985	1.17 (0.62–2.22)
Hallstrom et al. 1986	1.55 (0.98–2.45)
Vliestra et al. 1986	1.60 (0.89–2.86)
Hasdai et al. 1997	1.49 (0.89–2.51)
van Domburg et al. 2000	1.75 (1.30–2.37)
Liu et al. 2013	7.70 (0.87–68.27)
Sudden death	
Mulcahy et al. 1982	1.77 (1.23–2.54)
Vliestra et al. 1986	1.82 (1.14–2.89)
Gupta et al. 1993	1.48 (0.81–2.71)
Fatal reinfarction	
Mulcahy et al. 1982	1.68 (1.04–2.72)
Vliestra et al. 1986	1.78 (1.36–2.33)
Ischemic heart disease	
Salonen et al. 1980	1.60 (1.00–2.70)
Arrhythmic mortality	
Peters et al. 1995	1.80 (0.88–3.67)

Note: **CI =** confidence interval.

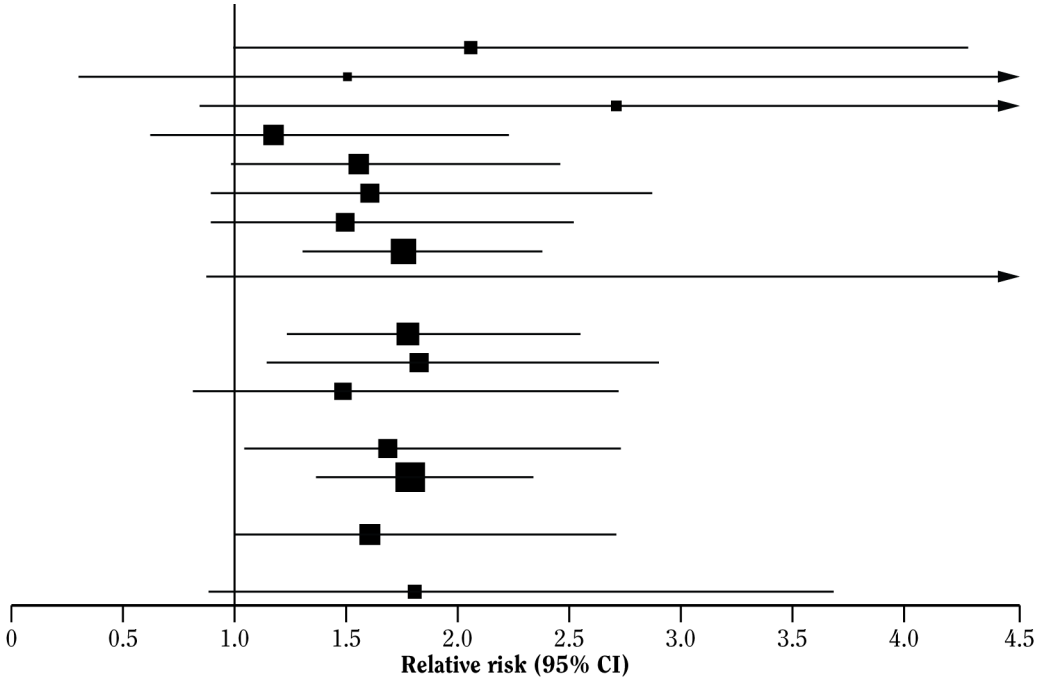
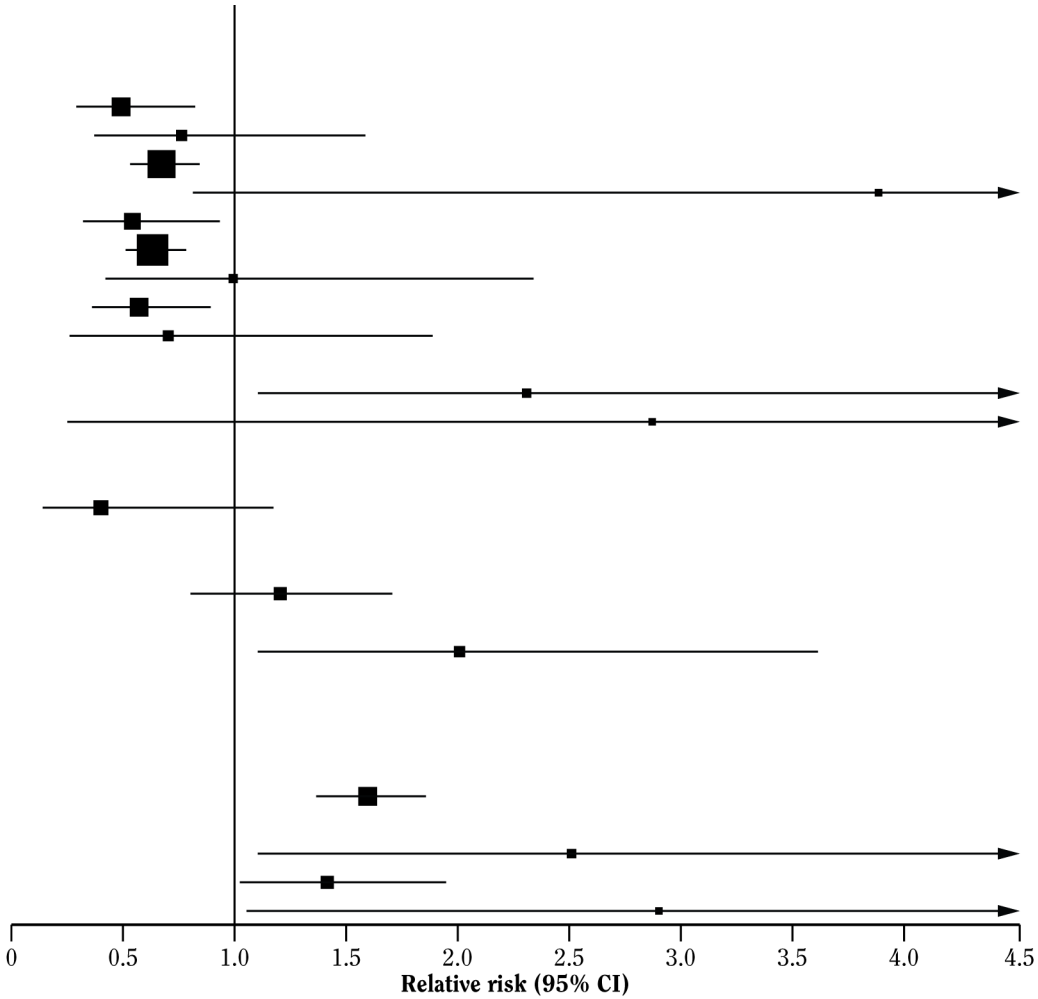


Figure 4.6 Comparison of incidence of new cardiac endpoints among persistent smokers and quitters

Study	Relative risk (95% CI)
Myocardial infarction or hospitalization or reinfarction	
Quit vs. persistent	
Wilhemsson et al. 1975	0.49 (0.29–0.82)
Sparrow et al. 1978	0.76 (0.37–1.58)
Aberg et al. 1983	0.67 (0.53–0.84)
Perkins et al. 1985	3.87 (0.81–18.37)
Rønnevik et al. 1985	0.54 (0.32–0.93)
Vliestra et al. 1986	0.63 (0.51–0.78)
Herlitz et al. 1995	0.99 (0.42–2.33)
Chow et al. 2010	0.57 (0.36–0.89)
Álvarez et al. 2013	0.70 (0.26–1.88)
Persistent vs. quit	
Voors et al. 1996	2.30 (1.10–5.10)
Choi et al. 2013	2.86 (0.25–33.04)
Stroke	
Quit vs. persistent	
Chow et al. 2010	0.40 (0.14–1.17)
Angina	
Persistent vs. quit	
Voors et al. 1996 (1- to 15-year follow-up)	1.20 (0.80–1.70)
Voors et al. 1996 (5- to 15-year follow-up)	2.00 (1.10–3.60)
Repeat procedures (CABG/PTCA/ vascularization)	
Quit vs. persistent	
Chen et al. 2012	1.59 (1.36–1.85)
Persistent vs. quit	
Voors et al. 1996	2.50 (1.10–5.90)
van Domburg et al. 2000	1.41 (1.02–1.94)
Liu et al. 2013	2.89 (1.05–8.00)



Note: **CABG =** coronary artery bypass grafting; **CI =** confidence interval; **PTCA =** percutaneous transluminal coronary angioplasty.

Summary of the Evidence

This review is the first Surgeon General's report to address the benefits of smoking cessation specifically in patients diagnosed with CHD. The importance of this topic is amplified by the fact that survival after a diagnosis of CHD has improved markedly during the past several decades (e.g., Savastano et al. 2014). Within this focus on the health benefits of cessation among patients already diagnosed with CHD, evidence was summarized on associations of cessation (versus persistent smoking) with all-cause mortality, deaths from cardiac causes and sudden death, and risk of recurrent or new cardiac events.

Methodologic Considerations

This review focused on direct evidence regarding the potential health benefits of smoking cessation—that is, quitting rather than continuing to smoke—among patients with CHD who were current smokers at the time of the index event. All the studies used in the review involved a prospective cohort, ensuring that the temporal relationship between cessation and outcome was correctly characterized. The evidence was abundant: Among the identified studies included in the evidence tables on the association between smoking cessation and important outcomes, there were 34 reports on all-cause mortality, 13 (yielding 20 distinct associations) on cause-specific mortality, and 15 on the risk of new or recurrent cardiac events. Thus, the strength with which inferences can be made is enhanced by the focus, quality, and scope of the evidence.

However, the potential role of confounding is a concern in drawing inferences from this body of evidence because (1) some associations considered were not adjusted for potential confounding variables and (2) among current cigarette smokers diagnosed with CHD, those who quit may have had a lower risk profile. A comparison of results from a study (Johansson et al. 1985) that used both unadjusted results and those that were adjusted for potential confounders indicated, however, that the adjusted results tended to be equal to or stronger than the unadjusted results. Thus, despite the potential for confounding to threaten the internal validity of the evidence, confounding is unlikely to have affected the validity of the overall evidence.

Compared with cohort studies in the general population, another noteworthy feature of follow-up studies of smoking cessation in patients with CHD is that the duration of follow-up tends to be shorter, sometimes only 6 months, and the median follow-up in this review was just 4.5 years. By contrast, 10 years was the median length of follow-up in cohort studies of smoking, in relation to all-cause mortality in the general population, that were included in the meta-analysis of Gellert and colleagues (2012). With a shorter duration of follow-up, fewer endpoints will be observed, and precision is reduced for estimating differences in outcome rates between quitters and persistent smokers.

Another caveat is that most studies included in this review relied on self-reports to determine smoking status; the results of two studies that compared biochemical assessments of smoking status with self-reported smoking suggest that relying on self-reported smoking alone can underestimate the true association (Twardella et al. 2006; Breitling et al. 2011a).

Evaluation of the Evidence

Causal Criteria

This Surgeon General's report is the first to consider the potential health benefits of smoking cessation in patients after a diagnosis of CHD. The report considers the totality of the evidence and references key criteria for causation established in the 1964 and 2004 Surgeon General's reports (U.S. Department of Health, Education, and Welfare [USDHEW] 1964; USDHHS 2004).

Temporality

The studies included in the evidence tables all had similar design features commonly used in prospective cohort studies. First, they studied patients who were current smokers when diagnosed with CHD. Second, patients were followed and reassessed to determine who quit smoking and who remained a smoker. Third, after quitters were distinguished from persistent smokers, there was subsequent follow-up for mortality and/or new cardiac events. Therefore, appropriate temporality is evident because, in all studies reviewed, smoking cessation preceded the occurrence of health outcomes in patients with CHD.

Consistency

The preponderance of the high-quality, focused bodies of evidence reviewed in this section showed that among patients who were current smokers when diagnosed with CHD, quitting smoking was consistently associated with reduced all-cause mortality compared with continuing to smoke. The studies focused primarily on MI as the index diagnosis, but they also included people with established CHD; the results were consistent regardless of the index condition. The studies were carried out

in a wide range of geographic locations; spanned several decades of research; and varied widely in methodology, such as sample size, timing of the measurement of change in smoking status, definition of quitters and persistent smokers, and control for potential confounding variables. Despite the potential for this variability to introduce inconsistencies across studies, a very clear, consistent set of results accrued over time. The evidence about cause-specific mortality and new or recurrent cardiac events also was highly consistent.

Strength of Association

The strength of the association observed for the outcome of all-cause mortality is best viewed in context of the existing evidence from the general population. The association between smoking and overall mortality was reviewed in the 1979 Surgeon General's report with a finding that the RR for overall mortality in cigarette smokers compared with nonsmokers was 1.7 (USDHEW 1979b), which is quite similar to an estimate arrived at in 2014 based on data in the 1964 Surgeon General's report (Schumacher et al. 2014). Because patients with CHD tend to be older than the general population, evidence specific to elderly populations is relevant. A systematic review of smoking and all-cause mortality in the elderly (defined as ≥60 years old) estimated a summary RR across studies of 1.83 (95% CI, 1.65–2.03) for current smoking versus never smoking (Gellert et al. 2012). Against this backdrop, the evidence for the association between smoking cessation and all-cause mortality in patients with CHD is of similar magnitude to findings from studies in the general population. In comparisons with persistent smokers, the median RR for all-cause mortality was 0.545 for those who quit smoking cigarettes; conversely, in reports that compared persistent smokers with quitters, the median RR was 1.67. The comparable magnitude of these associations is notable, considering that results for the general population are based on current versus never smokers, whereas the evidence reviewed here contrasts quitters with persistent smokers within a population made up entirely of current smokers at baseline.

The evidence presented for cause-specific mortality as an endpoint showed that, compared with quitting smoking, persistent smoking was strongly associated with increased mortality from cardiovascular disease endpoints and sudden death, with the median RR of 1.6 being very similar to that observed for all-cause mortality. Among patients with CHD who were current smokers when diagnosed, the risk of new or recurrent cardiac events was also observed to be strongly reduced by smoking cessation compared with persistent smoking; for example, the median RR for MI was 0.67.

When this body of evidence is viewed collectively, a consistent and coherent pattern of findings emerges showing that among patients with CHD who are smokers when they are diagnosed, compared with those who remain smokers, those who quit smoking have a reduced risk of (1) dying from all causes and, specifically, dying from cardiovascular disease or experiencing sudden death and (2) experiencing new or recurrent cardiac events. The observed associations were strong, and the magnitude of these associations is even more impressive when the methodologic issues discussed above that would tend to bias these associations toward the null are carefully considered.

Experiment

For drawing causal inferences, studies of smoking cessation interventions that include results for clinical endpoints provide very strong evidence. In what can be viewed as quasi-experimental evidence, a large-scale, observational prospective cohort study found a strong all-cause mortality benefit in patients diagnosed with MI who received an inpatient smoking cessation intervention compared with those who did not receive an inpatient smoking cessation intervention (Bucholz et al. 2017). Earlier, in a randomized controlled trial of an intensive smoking cessation intervention compared with usual care among patients diagnosed with acute coronary syndrome or decompensated heart failure, the intervention group experienced marked and statistically significant reductions in all-cause mortality and hospitalizations (Mohiuddin et al. 2007). Strong associations from an experimental study favor the likelihood of an actual direct and causal association and weigh against uncontrolled confounding as an explanation of the results of the observational studies. The studies that provide direct evidence on this question consistently indicate that compared with persistent smoking, smoking cessation leads to substantial decreases in all-cause mortality.

Specificity

The relevance of the criterion of specificity to the evidence considered in this report lies in the comparison of the results for cause-specific mortality with the results for all-cause mortality. These results are similar. A substantial reduction in all-cause mortality associated with smoking cessation that was paralleled by a similar reduction for specific cardiac causes of death provides evidence to support the conclusion that at least a portion of the health benefits of smoking cessation in patients with CHD results from reduced risk of death from cardiac causes. The mortality reduction experienced in quitters would also be expected to be present for other causes of death known to be caused by smoking, but the evidence base ascertained for this review provided little evidence on this question.

Coherence

The causal criterion of coherence weighed heavily in evaluating the overall body of evidence as to whether smoking cessation can be considered a cause of mortality reduction in patients with CHD. The evidence on mortality reduction in patients with CHD following cessation needs to be interpreted in the context of the larger body of evidence on smoking cessation in relation to mortality in the general population. Previous Surgeon General's reports have concluded that smoking causes increased all-cause mortality in the general population. Based on the causal criterion of coherence, smoking cessation would be expected to decrease all-cause mortality in patients with heart disease, as in the general population. Similarly, because active smoking is causally associated with many adverse cardiac endpoints, it would be expected a priori that smoking cessation in patients with CHD would be associated with reduced risk of developing recurrent CHD. The combination of the substantial body of evidence reviewed here, which documents that smoking cessation is associated with reduced risk of death and disease, along with the fact that this evidence is in accord with a priori expectations about the known adverse health effects of smoking in the general population, strengthens the argument inferring a causal association.

Further adding to the coherence of the evidence are the established roles of smoking in causing endothelial dysfunctions and increasing risk for thrombosis, two etiologic pathways that contribute substantially to ischemic heart disease (USDHHS 2010; Barua and Ambrose 2013; Vanhoutte et al. 2017). Increasing endothelial production of adhesion molecules and decreasing production of vasodilators are some known mechanisms through which smoking causes endothelial dysfunction (USDHHS 2010). In addition, through adverse effects on endothelial cells, as well as on platelets, fibrinogen, and coagulation factors, smoking increases the risk of thrombosis, a key mechanism in the pathogenesis of MI and stroke (USDHHS 2010; Barua and Ambrose 2013). McEvoy and colleagues (2015b) examined three sets of markers in participants in the Multi-Ethnic Study of Atherosclerosis (MESA): inflammatory biomarkers, vascular dynamics and function, and subclinical atherosclerosis. Inflammatory markers were lower in former smokers compared with current smokers, and a longer time since quitting was associated with lower inflammatory markers. Results from a few studies provide evidence that in current smokers diagnosed with heart disease, quitting smoking is associated with biomarker profiles of reduced risk compared with persistent smoking. For example, smoking cessation in patients with acute MI was associated with improved coronary endothelial function, an improvement not seen in nonsmokers (Hosokawa et al. 2008). Further, in patients with CAD, smoking cessation resulted in a reduced risk profile for macrophage cholesterol efflux (Song et al. 2015).

Synthesis of the Evidence

An extensive body of relevant evidence from prospective cohort studies was identified and reviewed. All studies were based on cohorts of patients who were current cigarette smokers when diagnosed with heart disease and who were followed up to first determine if they had quit smoking or continued to smoke and then to determine their vital status and to identify new or recurrent cardiac events. Most of this overall high-quality evidence indicates that in patients who are current smokers when diagnosed with heart disease, smoking cessation after the diagnosis is strongly and causally associated with reduced all-cause mortality. In patients with heart disease who are current smokers when diagnosed, the evidence indicates that smoking cessation reduces the risk of dying by almost one-half, a very strong clinical benefit. Not only is this unequivocally demonstrated in the data from prospective cohort studies, but the corroborating experimental evidence on this topic strongly reinforces this conclusion. Additionally, the evidence reviewed here demonstrates that the health benefits of smoking cessation after a heart disease diagnosis extend to mortality specifically from cardiac causes and sudden death. Third, the evidence indicates that smoking cessation is associated with decreased risk of new or recurrent cardiac events. Based on the causal criterion of coherence, the known causal associations between smoking and these outcomes in the general population support the causal nature of the associations.

Because all the currently available evidence is from prospective studies, the temporal nature of the association is not ambiguous. The evidence for each outcome showed a high degree of consistency across diverse study populations and measurement approaches. These characteristics of the evidence clearly indicate that in current smokers diagnosed with heart disease, smoking cessation is associated with reduced risk of all-cause mortality, cause-specific mortality, and new or recurrent cardiac events.

Conclusions

1. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between

smoking cessation and a reduction in all-cause mortality.

2. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between smoking cessation and reductions in deaths due to cardiac causes and sudden death.

3. In patients who are current smokers when diagnosed with coronary heart disease, the evidence is sufficient to infer a causal relationship between smoking cessation and reduced risk of new and recurrent cardiac events.

Implications

The evidence summarized in this section documents that cigarette smoking cessation has a profoundly positive impact on overall survival in patients who are current cigarette smokers when diagnosed with CHD. The reductions in risk are substantial for total mortality and cardiovascular disease-specific outcomes. Estimates across studies indicate that smoking cessation reduces relative risks for these outcomes by 30–40%. Considered in the context of current knowledge of the health benefits of smoking cessation in the general population, cessation of smoking would be expected to have major health benefits in patients diagnosed with CHD. This evidence has clear clinical implications. Current cigarette smokers who are diagnosed with CHD can improve their prognosis by quitting smoking. Providing evidence-based smoking cessation services to patients with CHD who smoke would be expected to have a substantial beneficial impact on their prognosis, with the magnitude of the benefits in some instances even equaling or exceeding that of other state-of-the-art therapies. A Cochrane review found evidence for efficacy of smoking cessation interventions in patients hospitalized for cardiovascular disease (Rigotti et al. 2012). The critical role of smoking cessation in cardiac rehabilitation is already recognized in evidence-based medicine guidelines (King et al. 2005; Smith et al. 2006); the new conclusions of this report can be cited in further emphasizing to the public health, clinical, and patient and caregiver communities just how critical it is to provide evidence-based smoking cessation services to cardiac patients. In particular, cardiologists who provide care to patients who have experienced cardiovascular events should (a) clearly communicate to these patients that quitting smoking is the most important action they can take to improve their prognosis and (b) offer patients evidence-based cessation treatments, including counseling, medications, and referral to more intensive assistance, including state quitlines (Fiore et al. 2008; U.S. Preventive Services Task Force 2015).

Chronic Respiratory Disease

Tobacco smoke contains thousands of chemical components that are inhaled and then deposited throughout the large and small airways and alveoli of the lungs (U.S. Department of Health and Human Services [USDHHS] 2010). The toxic components of cigarette smoke injure the lungs through a variety of mechanisms, including oxidative injury and inflammation, carcinogenesis, and effects on the immune system (USDHHS 2010, 2014). For example, acrolein and formaldehyde impair ciliary clearance and nitrogen oxides cause inflammation of the airways, while cadmium and hydrogen cyanide result in direct oxidant injury and impaired oxidative metabolism (USDHHS 2010). Cigarette smoke initiates an inflammatory process that results in direct destruction of lung parenchyma that is mediated through (a) the release of proteinases that damage the extracellular matrix of the lung, (b) apoptosis because of oxidative stress, and (c) loss of matrix–cell attachment and ineffective repair of elastin and other extracellular matrix components that enlarge the airspace (USDHHS 2010, 2014). Although successful smoking cessation ends daily exposure to innumerable injurious compounds, the prolonged deleterious effects of tobacco smoke result in irreversible impairment in immune responses, changes in the makeup of the lung microbiome, and continued lung injury even after cessation (USDHHS 2014).

This section provides an update on the evidence about smoking cessation and respiratory health among persons with chronic obstructive pulmonary disease (COPD) or asthma.

Conclusions from Previous Surgeon General's Reports

Associations of cigarette smoking with chronic respiratory diseases, including COPD, asthma, and interstitial lung diseases, have been addressed in numerous Surgeon General's reports since 1964 (U.S. Department

of Health, Education, and Welfare [USDHEW] 1964). The 1964 report concluded that cigarette smoking is the most important cause of chronic bronchitis (USDHEW 1964). The principal topic of the 1984 report was COPD (USDHHS 1984), and later reports addressed active smoking, exposure to secondhand smoke, and major respiratory diseases (USDHHS 2004, 2006, 2014). The conclusions from these reports addressed the causation and exacerbation of chronic respiratory disease by tobacco smoking; the risks of respiratory infections, a frequent contributor to exacerbation of chronic respiratory diseases; and the benefits of cessation (USDHEW 1964; USDHHS 1984). Several Surgeon General's reports have addressed the health benefits of smoking cessation for COPD; these conclusions are listed in Table 4.25.

Literature Review Methods

MEDLINE, SCOPUS, and EMBASE were searched for studies that focused on smoking cessation and COPD or asthma and were published between January 1, 2008, and May 26, 2016. A systematic literature search was created for PubMed and translated to the EMBASE and SCOPUS databases. A combination of controlled vocabulary and keyword terms was used for each of the following concepts: (1) smoking cessation, (2) respiratory phenomena, (3) asthma, (4) chronic obstructive pulmonary disease, (5) emphysema, and (6) chronic bronchitis. Studies that did not focus on smoking cessation were excluded. To formulate conclusions, evidence cited in the 2014 Surgeon General's report on smoking was considered along with any newly available evidence. Search results were limited to studies published in English and to original research. The primary search identified 1,977 items. Two independent reviewers identified 45 articles through consensus after reviewing the titles and abstracts. After a full review of the 45 articles, 24 articles (17 on COPD and 7 on asthma) were selected as relevant for this update.

Chronic Obstructive Pulmonary Disease

This section addresses advances in the evidence base on COPD and smoking cessation and the implications of the new findings. Our current understanding of the pathogenesis of COPD underscores the importance of smoking cessation in slowing and eventually ending lung damage associated with tobacco smoke. The occurrence of clinical

Table 4.25 Conclusions about smoking cessation and chronic respiratory disease from previous Surgeon General's reports

Report	Conclusions
USDHHS (2010, p. 10)	• Smoking cessation remains the only proven strategy for reducing the pathogenetic processes leading to chronic obstructive pulmonary disease.
USDHHS (1990, p. 11)	• Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking. • For persons without overt chronic obstructive pulmonary disease (COPD), smoking cessation improves pulmonary function about 5 percent within a few months after cessation. • Cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers. • With sustained abstinence, the COPD mortality rates among former smokers decline in comparison with continuing smokers.
USDHHS (1984, p. 10)	• Cessation of smoking leads eventually to a decreased risk of mortality from COLD compared with that of continuing smokers. The residual excess risk of death for the ex-smoker is directly proportional to the overall lifetime exposure to cigarette smoke and to the total number of years since one quit smoking. However, the risk of COLD mortality among former smokers does not decline to equal that of the never smoker even after 20 years of cessation.
USDHEW (1979a, p. 18)	• Cessation of smoking definitely improves pulmonary function and decreases the prevalence of respiratory symptoms. Cessation reduces the chance of premature death from chronic bronchitis and emphysema.

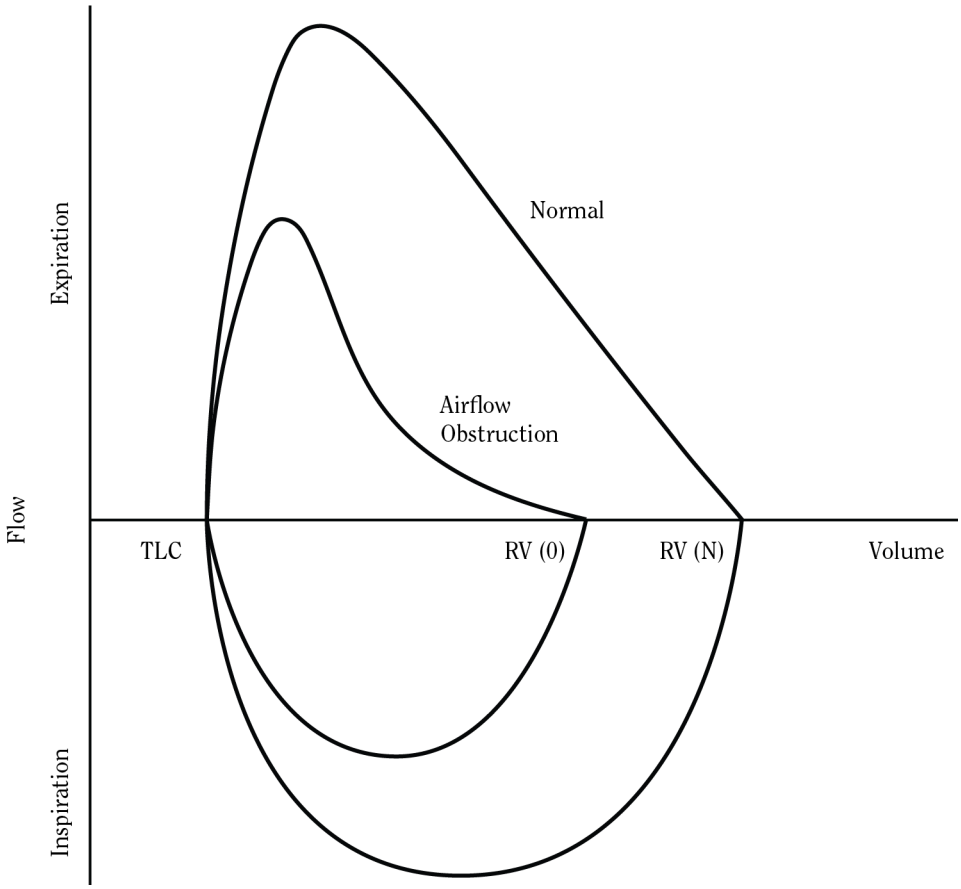
Notes: **COLD =** chronic obstructive lung disease; **COPD =** chronic obstructive pulmonary disease; **USDHEW =** U.S. Department of Health, Education, and Welfare; **USDHHS =** U.S. Department of Health and Human Services.

COPD reflects a long course of progressive deterioration of lung function that can begin before conception, as maternal smoking during pregnancy affects the development of lungs in fetuses (Cook et al. 1998; Checkley et al. 2010, 2016).

COPD is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (Celli et al. 2004; USDHHS 2014; Benditt n.d.) (Figure 4.7). The development of airflow limitation among those with COPD is usually progressive and reflects the ongoing processes of lung injury that are initiated and sustained by persistent exposure to tobacco smoke (Rabe et al. 2007). Thus, smoking cessation is critical in preventing COPD, slowing its progression, and treating this disorder. Although previous definitions have focused on phenotypes of COPD, such as chronic bronchitis and emphysema, the diagnosis of COPD has now been standardized on the basis of spirometry and the presence of airflow obstruction (i.e., a reduced ratio of forced expiratory volume at 1 second [FEV_1] to forced vital capacity [FVC]) that does not fully reverse after bronchodilation (Tashkin and Murray 2009). Previously, COPD was defined by a fixed ratio (post-bronchodilator $FEV_1/FVC < 70\%$) (Rabe et al. 2007). There is debate, however, on using the lower limit of normal for selected reference populations as the best approach to standardizing the interpretation of spirometry results by accounting for age, sex, height, and race (Mannino et al. 2007; Swanney et al. 2008; Miller et al. 2011b; Mannino and Diaz-Guzman 2012; Quaderi and Hurst 2017).

Thus, FEV_1/FVC is generally used to define COPD, but FEV_1 and the rate of decline of FEV_1 have been the two most widely used outcome measures for clinical trials related to COPD. These indicators are also associated

Figure 4.7 Flow-volume loops for a person with (obstruction) and without (normal) chronic obstructive pulmonary disease



Source: Benditt (n.d.). Copyright © University of Washington, 2004.
Note: **RV =** residual volume; **TLC =** total lung capacity.

with measures of health-related quality of life and mortality (Wise 2006). Additionally, however, there is evidence to support the presence of considerable smoking-related respiratory disease among persons with normal lung function. For example, in a study by Woodruff and colleagues (2016), half of current or former smokers with preserved pulmonary function exhibited respiratory symptoms, and former smokers with preserved lung function had higher rates of exacerbation events than lifelong nonsmokers. Sensitive imaging approaches are now used to quantify changes in the lungs, including emphysema, that have health implications. Oelsner and colleagues (2014) found higher all-cause mortality among former and current smokers with emphysematous changes on computed tomography (CT) and preserved pulmonary function. However, the analysis did not find differences in the risk of having such changes by smoking status.

Smoking Cessation and Chronic Obstructive Pulmonary Disease

Cigarette smoking is the most common cause of COPD in the United States (Xu et al. 1992; Anthonisen et al. 1994; Perret et al. 2014) and is a consistent and strong risk factor for the development of COPD (USDHHS 2014). In the United States, the population-attributable risk for developing COPD caused by smoking has been estimated to be as high as 80–90% (Eisner et al. 2010; USDHHS 2014). Although observational evidence shows that air pollution adversely affects persons with COPD, not starting to smoke and smoking cessation remain the only proven prevention strategies for reducing the risk of developing chronic respiratory diseases caused by cigarette smoking (Xu et al. 1992; Anthonisen et al. 1994; Abramson et al. 2015). Smoking cessation can prevent or delay the development of airflow limitation and slow the progression of chronic respiratory disease; it is the only intervention that has been shown to reduce the rate of FEV_1 decline in both men and women (Thomson et al. 2004) and to reduce all-cause mortality among those with COPD (Anthonisen et al. 2005).

Epidemiology of Mortality from Chronic Obstructive Pulmonary Disease in Relation to Tobacco Cessation

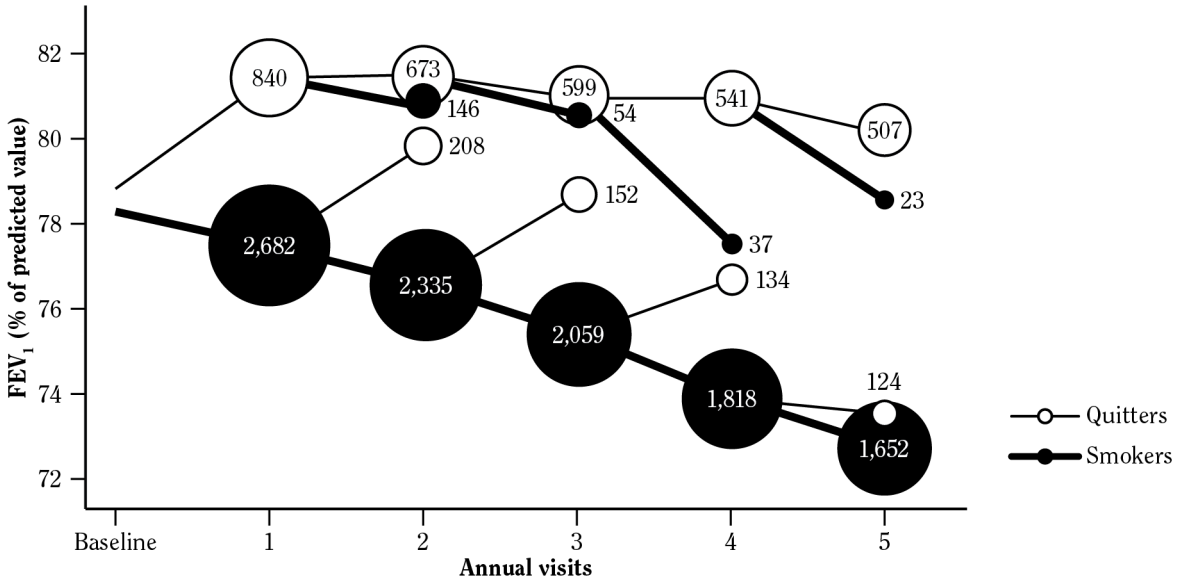
The relationship between temporal trends in the decline of smoking prevalence and trends in COPD morbidity and mortality is complex, as evidenced by data collected in the United States (Mannino and Buist 2007). Prevalence estimates of COPD have limited validity because symptoms related to COPD, such as dyspnea on exertion and limitation in physical activity, are nonspecific (Tashkin and Murray 2009). Nonetheless, some trends are quickly apparent from surveillance data. Among all U.S. adults, age-adjusted mortality from COPD increased from 29.4 per 100,000 population in 1968 to 67.0 per 100,000 population in 1999 and then declined slightly to 63.7 per 100,000 population in 2011 (Ford 2015). Mortality from COPD among men has declined since 1999, but among women, the age-adjusted mortality continues to increase (Ford 2015). Despite this narrowing of the difference between men and women, mortality rates in men continue to exceed those in women (Ford 2015). Notably, among certain population subgroups (i.e., Black men, White men, adults 55–64 years of age, adults 65–74 years of age), mortality rates have declined during the past decade (Ford 2015).

How Smoking Cessation Affects the Decline of Lung Function in Smokers

The 1990 Surgeon General's report on the health benefits of smoking cessation cited only three studies concerning the effect of smoking cessation on the decline of lung function (USDHHS 1990). The 1990 report did provide a conclusion that "With sustained abstinence from smoking, the rate of decline of pulmonary function in former smokers returns to that of never smokers" (USDHHS 1990, p 349). Since the 1990 report, both clinical and population studies have examined the association between cessation of tobacco smoking and the decline of lung function.

The Lung Health Study, a randomized clinical trial of smoking cessation and respiratory outcomes, evaluated the effect of an intensive smoking cessation intervention (combined randomly with either the inhaled bronchodilator ipratropium bromide or placebo) on the rate of FEV_1 decline among 5,887 cigarette smokers 35–60 years of age with mild-to-moderate airflow limitation from COPD (Anthonisen et al. 1994). Participants who continued to smoke had a greater decline in FEV_1 at the 5-year follow-up (Figure 4.8) compared with those who quit. In a separate analysis of data from the Lung Health Study, a decrease in the number of cigarettes smoked by continued smokers did not reduce the rate of decline of lung function compared with complete cessation, unless the number of cigarettes smoked was reduced by at least 85% (Simmons et al. 2005). The benefit of a lower decline of FEV_1 among participants in the smoking intervention program compared with the control group persisted over 11 years of follow-up (Anthonisen et al. 2002; Murray et al. 2002). Participants in the smoking intervention group had a lower decline of FEV_1 than participants receiving usual care (the control group) (Anthonisen et al. 2002). Men who quit smoking at the beginning of the Lung Health Study had a rate of decline in FEV_1 of 30.2 milliliters (mL)/year, whereas this measure declined at 21.5 mL/year in women

Figure 4.8 Impact of smoking cessation and resumption on FEV_1 decline in the Lung Health Study cohort of patients with chronic obstructive pulmonary disease



Source: Scanlon and colleagues (2000, p. 384). Reprinted with permission of the American Thoracic Society. Copyright © 2018 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

Note: **FEV_1 =** forced expiratory volume at 1 second.

who quit. Men who continued to smoke throughout the 11 years of follow-up experienced an FEV_1 decline of 66.1 mL/year, and women who continued to smoke experienced a decline of 54.2 mL/year (Anthonisen et al. 1994). At the 14.5-year follow-up, all-cause mortality was lower in the intervention group than in the usual-care group (8.8 per 1,000 person-years vs. 10.4 per 1,000 person-years, p = 0.03) (Anthonisen et al. 2005).

Several studies have examined how quickly benefits of smoking cessation are observed. In an analysis of a 6-year follow-up of 4,451 Japanese American men participating in the Honolulu Heart Program, Burchfiel and colleagues (1995) reported that the rate of FEV_1 decline was reduced in participants who quit smoking compared with those who continued smoking. These researchers also found that, after 2 years of successful cessation, the reduced rate of FEV_1 decline among quitters approximated that of participants who never smoked. In contrast, the rate of FEV_1 decline in the first 2 years was similar between quitters and those who continued to smoke. This last finding suggests that the effects of smoking cessation on decline in lung function are not immediate and may take up to 2 years to be manifested.

Table 4.26 summarizes reports published in 2009 or later offering further evidence on smoking cessation and the natural history of COPD and other respiratory outcomes from long-term studies. Studies and trials have continued to demonstrate immediate improvement in self-reported respiratory symptoms at 1 to 3 months after cessation (Louhelainen et al. 2009; Etter 2010) and an improvement in FEV_1 and in COPD-specific outcomes at 1 year after quitting (Tashkin et al. 2011; Dhariwal et al. 2014). Smoking cessation has a beneficial effect at any age, although the benefit was found to be more pronounced among persons who quit before 30 years of age compared with those who quit after 40 years of age (Kohansal et al. 2009).

Although smoking cessation results in less severe respiratory symptoms, the inflammatory burden may persist. In a prospective cohort, Louhelainen and colleagues (2009) found oxidant and protease burden in airways (using sputum as a proxy to measure airway inflammation) that persisted for months after smoking cessation. Versluis and colleagues (2009) found that adenosine receptor mechanisms may be implicated in the progression of the inflammatory response after cessation in cigarette smokers with COPD. Specifically, the expression of adenosine receptors increased in some sputum cell types and sputum adenosine levels appeared to rise in those with COPD 1 year after smoking cessation (Versluis et al. 2009).

Table 4.26 Studies on smoking cessation and chronic obstructive pulmonary disease, 2009–2017

Study	Design/population	Findings
Lung function		
Kohansal et al. (2009)	• Prospective cohort • 4,391 participants 13–71 years of age with two or more valid spirometry measurements during follow-up periods (1971–1997) of the Framingham Offspring Study • Participants divided into three groups: – Never smokers (n = 1,578) – Continuous smokers (n = 754) – Other smokers, which included former smokers (n = 2,059) • Never smokers and continuous smokers were further divided into categories of healthy and nonhealthy	Smoking cessation had a beneficial effect at any age, but it was more pronounced in earlier quitters The rate of FEV_1 decline in both male and female smokers who quit before age 30 was indistinguishable from healthy never smokers In contrast, smokers who quit after 40 years of age showed a significantly enhanced rate of decline of FEV_1 versus healthy never smokers and earlier quitters, but their rate was not significantly different from that of continuous smokers The mean FEV_1 decline value among continuous smokers (with 95% CI) was 38.2 ml (33.9–42.6) for males and 23.9 ml (20.9–27.0) for females, with p = 0.001 for male vs. female (p ≤0.05 versus healthy never smokers)
Louhelainen et al. (2009)	• Prospective cohort • 61 smokers: – 21 with chronic bronchitis or COPD – 15 with asthma – 25 asymptomatic • Followed 3 months after smoking cessation	Although symptoms improved after smoking cessation, oxidant and protease burden in the airways continued for months after cessation
Takabatake et al. (2009)	• Prospective cohort • 82 former smokers with COPD • Followed for 30 months	*CDC6* may be one of the susceptibility genes that contributes to rapid decline in lung function despite smoking cessation in patients with COPD
Versluis et al. (2009)	• Prospective cohort • 26 smokers who had successfully quit for at least 1 year: – 11 with COPD – 15 asymptomatic • Followed at 1 year after cessation	Adenosine-related effector mechanisms are involved in the persistence and progression of the inflammatory response in COPD after 1 year of smoking cessation
Mazur et al. (2011)	• Prospective cohort • 474 current smokers • 155 with COPD symptoms • 319 no symptoms • Followed for 2 years, with 111 succeeding in cessation	After 2 years of follow-up, levels of surfactant protein A were higher in those who continued smoking compared with those who quit
Tashkin et al. (2011)	• Randomized controlled trial • 504 participants (smokers with mild-to-moderate COPD: – 250 in the varenicline treatment group – 254 in the placebo treatment group	In this 1-year cessation trial of smokers with COPD, continuous abstinence compared with continuous smoking significantly improved (p = 0.0069) mean change from baseline in post-bronchodilator FEV_1 (although the difference subsequently narrowed) and total scores on the Clinical COPD Questionnaire at 12 weeks, with sustained improvement thereafter on that instrument
Dhariwal et al. (2014)	• Prospective cohort • 358 heavy smokers screened: – 38 with COPD – 55 with normal spirometry • Control group: 19 nonsmokers • Followed for 1 year	Smoking cessation had differential effects on lung function (FEV_1 and gas transfer) and features revealed on high-resolution CT images (emphysema and micronodules) Smoking cessation in patients with COPD caused transient improvement in FEV_1 and decreased the presence of micronodules

Table 4.26 Continued

Study	Design/population	Findings
Lung function (continued)		
Ito et al. (2015)	• Cross-sectional • 93 participants divided into four groups: – Former smokers with COPD (n = 23) – Smokers with COPD (n = 17) – Current smokers (n = 27) – Nonsmokers (n = 26)	One year after smoking cessation, participants with COPD had improved mucociliary clearance
Respiratory symptoms		
Etter (2010)	• Prospective cohort • Visitors to Stop-tabac.ch website • 18 years of age or older • 15,916 participants at baseline • 1,831 participants at 1-month follow-up	Smoking cessation was followed by a rapid and substantial improvement in self-reported respiratory symptoms In the 252 baseline smokers who had quit smoking at 30-day follow-up, there was a substantial decrease in the proportion of participants who declared that they often coughed even without a cold (from 51.6% at baseline to 15.5% at follow-up), expectorated when they coughed in the morning (from 47.6% to 19.4%), were out of breath after climbing stairs or after a quick walk (from 75.0% to 48.4%), and who had a wheezing respiration (from 33.7% to 10.3%) (p = 0.001 for all before/after comparisons)
Josephs et al. (2017)	• Retrospective cohort • 16,479 patients with COPD with outcomes over 3 years • 8,941 former smokers	Former smokers had significantly reduced risk of death, hospitalization, and visits to the emergency department Compared with active smokers, ex-smokers had significantly reduced risk of death, with a hazard ratio (95% CI) of 0.78 (0.70–0.87); hospitalization, 0.82 (0.74–0.89); and emergency department attendance, 0.78 (0.70–0.88)
Imaging		
Ashraf et al. (2011)	• Prospective cohort • 726 current and former smokers • Aged 50–70 years • Smoking history of more than 20 pack-years. • Former smokers were only included if they had quit smoking after the age of 50 years and less than 10 years before inclusion. • All subjects had to have an FEV_1 at least 30% of predicted normal. • Followed for more than 2 years	Current smoking status was associated with lower lung density and a difference in lung density between current and former smokers who were observed at baseline, which corresponded closely to changes in lung density after cessation After smoking cessation (n = 77) 15th percentile density (PD15) decreased by 6.2 g/l (p < 0.001) in the first year, and by a further 3.6 g/l (p < 0.001) in the second year, after which no further change could be detected; moreover, the first year after relapse to smoking (n = 18) PD15 increased by 3.7 g/l (p = 0.02)
Miller et al. (2011a)	• Prospective cohort • 10 former smokers with COPD after 4 years of not smoking	Cessation of tobacco smoking in heavy smokers with moderately severe emphysema was associated with evidence of persistent airway inflammation and progression of emphysema on CT
Shaker et al. (2011)	• Prospective cohort • 36 former smokers with COPD • Followed for 2–4 years	Inflammation partly masked the presence of emphysema on CT, and smoking cessation resulted in a paradoxical fall in lung density, which resembled rapid progression of emphysema; this fall in density likely resulted from an anti-inflammatory effect of smoking cessation

Table 4.26 Continued

Study	Design/population	Findings
Imaging (continued)		
Hoesein et al. (2013)	• Prospective cohort • 3,670 male smokers • 1- and 3-year follow-up • Follow-up CT and pulmonary testing	Current smokers had yearly FEV_1 decline of 69 mL, and participants who had quit smoking more than 5 years earlier had a yearly decline of 57.5 mL Compared with current smokers, participants who had quit smoking more than 5 years earlier showed significantly lower rates of progression of emphysema on CT
Hlaing et al. (2015)	• Prospective cohort • 45 persons with COPD who stopped smoking • Followed for 1 year	On the CT image, significant decreases occurred in mean lung density and the attenuation value separating the least 15% pixels, but there was a significant increase in the percentage of the relative area of the lungs with attenuation values <-950 Hounsfield units
Takayanagi et al. (2017)	• Prospective cohort • 58 patients with COPD at the time of their enrollment at the hospital and 2 years later	Airway disease and vascular remodeling may be reversible to some extent through smoking cessation and appropriate treatment
Immunity		
Roos-Engstrand et al. (2009)	• Case-control • 19 persons with stable COPD: – 7 smokers – 12 former smokers • Compared with 12 age-matched never smokers and 13 pack-years-matched smokers with normal lung function	Five years after smoking cessation, former smokers with COPD had significantly higher percentages of CD8+ cells compared with never smokers
DNA methylation		
Tsaprouni et al. (2014)	• Cross-sectional • Discovery cohort: 464 participants who were either diagnosed with CAD (n = 238) or were considered healthy (controls, n = 226): – Current smokers (n = 22) – Former smokers (n = 263) – Never smokers (n = 179) • Replication cohort: 356 female participants, all twins: – Current smokers (n = 41) – Former smokers (n = 104) – Never smokers (n = 211)	The effect of smoking on DNA methylation was partially reversible following smoking cessation for longer than 3 months
Wan et al. (2012)	• Cross-sectional • Discovery cohort: 1,085 participants with ≥5 pack-years of cigarette smoking and reported FEV_1 limitation, as well as one eligible sibling with ≥5 pack-years of cigarette smoking: – Current smokers (n = 396) – Former smokers (n = 689) • Replication cohort: 369 participants with FEV_1 limitation: – Never smokers (n = 68) – Current smokers (n = 103) – Former smokers (n = 198)	The existence of dynamic, site-specific methylation changes in response to smoking may contribute to the risks associated with cigarette smoking that persist after cessation

Notes: **CI =** confidence interval; **COPD =** chronic obstructive pulmonary disease; **CT =** computed tomography; **FEV_1 =** forced expiratory volume at 1 second; **CAD =** coronary artery disease; **mL =** milliliter.

In a later study, Mazur and colleagues (2011) assessed levels of surfactant protein A (SP-A) among smokers, nonsmokers, and former smokers over a 2-year period. Although plasma SP-A levels tended to decline among those who quit smoking, no significant difference from baseline was evident at the 2-year follow-up. A difference in plasma SP-A levels was evident, however, between those who quit and active smokers, whose SP-A levels continued to increase (Mazur et al. 2011).

Novel Diagnostics for Assessing the Impact of Smoking Cessation on the Progression of Chronic Obstructive Pulmonary Disease

Since the earlier Surgeon General's reports on this topic (USDHHS 1984, 2004), new techniques—such as imaging—have been used to investigate the natural history of COPD. These techniques have provided insights into structural changes and genomics, epigenomics, and other "-omics" approaches that help to better understand the molecular determinants of COPD risk and the persistence of risk after cessation. Furthermore, novel therapeutic options—such as epigenetic regulation—can be reprogrammed, potentially modifying risk and supporting treatment of disease states (Sakao and Tatsumi 2011).

Imaging

Quantitative volumetric CT scanning, a well-established diagnostic modality, can assess pathology in vivo, enabling morphologic phenotyping of three critical components of the progression of COPD: emphysema (Bankier et al. 2002; Madani et al. 2008), thickening of the airway wall (Orlandi et al. 2005; Coxson 2008), and trapping of expiratory air (Mets et al. 2012). These measures correlate with pathologic measures of emphysema and small airways disease and predict such clinical outcomes as FEV_1 decline (Mohamed Hoesein et al. 2011) and frequency of exacerbation (Han et al. 2011). Additionally, the growing adoption of annual CT scans to screen for lung cancer makes possible volumetric analysis at a population level over time, providing a powerful tool for assessing changes in lung structure after cessation of exposure to tobacco smoke, at least in this high-risk group. Low-dose CT used in annual screening enables the assessment of airways and lung parenchyma with less radiation compared with conventional CT scanning. Examining the effects of cessation on volumetric CT imaging is complicated, however, by the contradiction between the reported short-term and long-term effects of smoking. Specifically, previous studies have demonstrated that current cigarette smoking increases measurements of lung density and that these changes are most likely a result of accumulation of particulate matter resulting in inflammation (Grydeland et al. 2009), but over the long term, the emphysematous changes related to inhaling tobacco smoke result in low lung density (Ashraf et al. 2011). It is important that changes in lung density over the short term not be interpreted as either the progression of emphysema or improvement in that condition. Smoking cessation has been shown to reduce lung density, and the rate of reduction increases at 2 years post-cessation (Scanlon et al. 2000; Ashraf et al. 2011). At 2 years post-cessation, lung density stabilizes, suggesting a reversal of the inflammatory sequelae of exposure to tobacco smoke, which is consistent with findings on lung function in the Lung Health Study (Scanlon et al. 2000; Ashraf et al. 2011). A similar study by Takayanagi and colleagues (2017) demonstrated progression of emphysema, particularly in the subgroup of patients with exacerbations, but imaging findings related to airway disease and pulmonary vasculature did not change in proportion to the progression of emphysema.

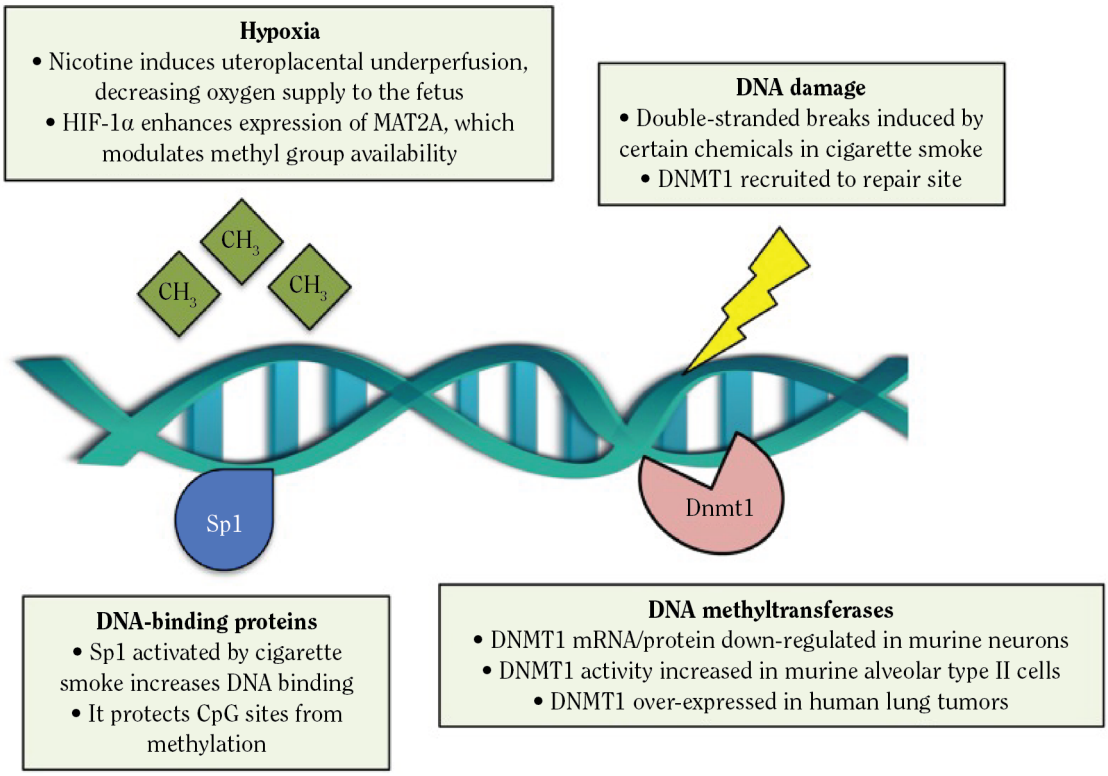
Advances in Epigenetics

Epigenetics is defined as the study of mechanisms that cause heritable changes in gene expression rather than alterations in the underlying sequence of deoxyribonucleic acid (DNA) (Dupont et al. 2009). Epigenetics can help measure the extent to which gene expression is altered in response to environmental exposure. Because epigenetics is a dynamic process, tracking the epigenome over time in relation to smoking cessation becomes relevant. Recent studies have demonstrated a role of DNA methylation, one of the main forms of epigenetic modification, in the pathways of smoking and smoking-induced diseases via the regulation of gene expression and genome stability (Figure 4.9). Methylation may underlie disease-specific gene expression changes, and characterization of these changes is a critical first step toward the identification of epigenetic markers and the possibility of developing novel epigenetic therapeutic interventions for COPD (Vucic et al. 2014).

Smoking alters the bronchial airway epithelial transcriptome and induces expression of genes involved in the regulation of oxidative stress, xenobiotic metabolism, and oncogenesis while suppressing those involved in the regulation of inflammation and tumor suppression (Spira et al. 2004). DNA methylation studies have been performed on a range of samples, including whole-blood homogenates and cells obtained from bronchial brushing and buccal swabbing (Breitling et al. 2011b; Tsaprouni et al. 2014; Guida et al. 2015; Wan et al. 2015).

An increasing number of smoking-related CpG sites (sites with a cytosine nucleotide next to a guanine nucleotide in the linear sequence) in various genes—such as aryl-hydrocarbon receptor repressor *(AHRR),* coagulation factor II receptor-like 3 *(F2RL3),* and G protein-coupled

Figure 4.9 Cigarette smoking and DNA methylation



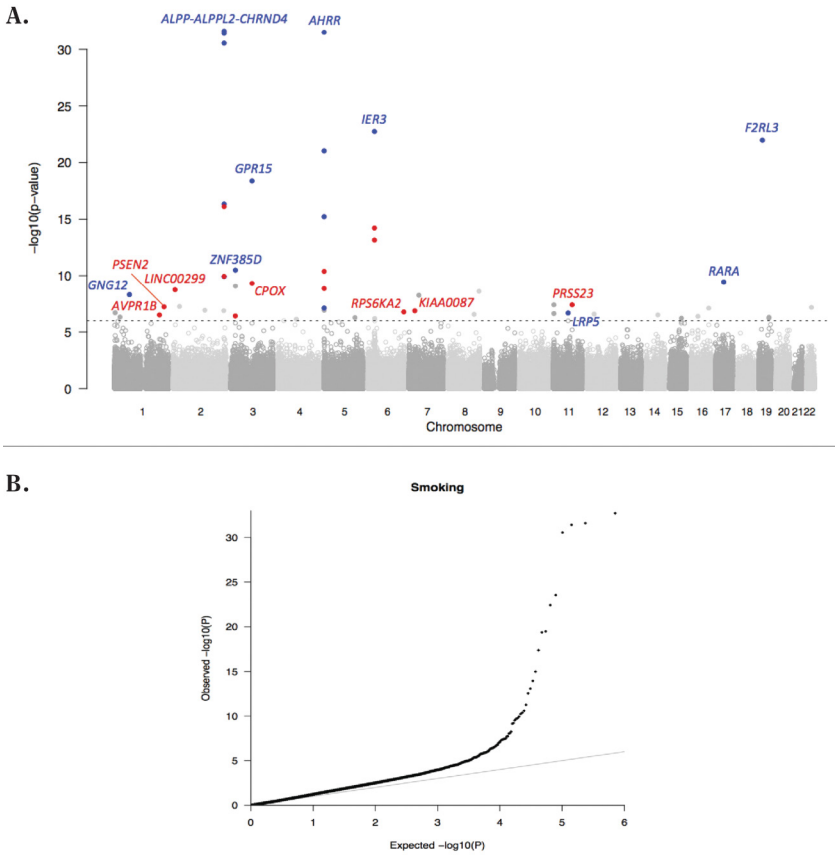
Source: Lee and Pausova (2013). Copyright © 2013 Lee and Pausova.

receptor 15 *(GPR15)*—have been discovered by epigenome-wide association studies based on samples of whole blood; these markers have shown utility as quantitative biomarkers of current and past smoking exposure and predictors of smoking-related disease risk (Figure 4.10) (Breitling et al. 2011b; Tsaprouni et al. 2014; Guida et al. 2015). Breitling and colleagues (2011b) found that DNA methylation was significantly lower in smokers than nonsmokers (percent difference in methylation = 12%; $p = 2.7 \times 10^{-31}$) in *F2RL3* and correlated negatively with the number of smoked cigarettes and positively with the duration of smoking abstinence. Similar exposure-related differences in the methylation of this gene were seen in another study, with the intensity of *F2RL3* methylation increasing gradually in long-term (>20 years) quitters to levels similar to that of never smokers (Zhang et al. 2014).

Guida and colleagues (2015) conducted epigenome-wide association studies to capture the dynamics of smoking-induced epigenetic changes after smoking cessation using genome-wide methylation profiles obtained from blood samples in 745 women from two European populations. The authors found that *LRRN3* also was significantly overexpressed in current smokers as compared with never smokers (fold change = 2.85; $p = 2.1 \times 10^{-24}$). Similar to the findings of Breitling and colleagues (2011b), Guida and colleagues (2015) demonstrated a dose-response relationship between methylation and time since cessation. The expression of only one additional gene, *FOXO3*, was found to be upregulated in current smokers (fold change = 1.27; $p = 4.3 \times 10^{-6}$) (Guida et al. 2015).

Wan and colleagues (2012) assessed the impact of DNA methylation after smoking cessation over time among those in the International COPD Genetics Network (n = 1,085), followed by replication in the Boston Severe Early Onset COPD study (n = 369). These investigators identified a novel locus *(GPR15)* associated with cigarette smoking and found evidence to suggest that the existence of smoking-related, site-specific methylation changes may contribute to extended risks associated with cigarette smoking after cessation. Among former smokers, participants with the highest cumulative exposure to smoke and shortest duration of smoking cessation had the lowest mean methylation, but participants with the lowest cumulative exposure to smoke and the longest duration of cessation had the highest mean methylation, suggesting a dose-dependent response. Tsaprouni and colleagues

Figure 4.10 Epigenome-wide association study Manhattan plot and Q-Q plot for smoking status in the Cardiogenics Cohort



Source: Tsaprouni and colleagues (2014), with permission.
Note: In Panel A, the vertical axis indicates (-log10 transformed) observed *p values*, and the dotted horizontal line indicates the threshold of significance ($p = 10^{-6}$) to select markers for replication. Previously reported loci are indicated in blue, and new loci and new signals in known loci are marked in red. Panel B illustrates the distribution of the *p* values.

(2014) showed that the effect of smoking on DNA methylation was partially reversible following cessation of more than 3 months. That study additionally used whole-blood, ribonucleic acid (RNA) sequencing to demonstrate evidence of the higher expression of *PSEN2, PRSS23, RARA, F2RL3, GPR15, CPOX, AHRR,* and *RPS6KA2* genes among former and current smokers. Only *GPR15* showed a clear trend of higher gene expression in smokers compared with nonsmokers, suggesting that a reduction in methylation levels observed in smokers leads to higher levels of RNA transcription (Tsaprouni et al. 2014).

Advances in Proteomics

Smoking-related inflammation secondary to lung disease has been well described in earlier reports (USDHHS 2014). The 2014 Surgeon General's report concluded that sufficient evidence exists to infer that components of cigarette smoke affect the immune system and that some of these effects are immune system activating, while others are immunosuppressive (USDHHS 2014). Alterations in innate and adaptive immunity result in both emphysema and airway remodeling, and a range of pathways for inflammatory biomarkers related to smoking have been described (Ito et al. 2006; USDHHS 2014). Profiles of inflammatory biomarkers change after smoking cessation. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (Coxson et al. 2013) found that several circulating biomarkers were associated with both the severity (SP-D, soluble receptor for advanced glycation end products [sRAGE], *CCL18*) and progression (SP-D, sRAGE, fibrinogen, interleukin [IL] 6, and CRP) of emphysema assessed by volumetric

CT imaging. Circulating biomarkers may provide an additional proxy for lung inflammation and emphysematous change. SP-D, one of several surfactant proteins, is thought to be related to pulmonary immunity (Kishore et al. 2006) and is higher in persons with COPD (Lomas et al. 2009). This relative increase is believed to reflect, in part, inflammation in the lung leading to degradation and leakage into the circulation. sRAGE is thought to protect against inflammation, and low levels of sRAGE have been associated with several inflammatory diseases, such as diabetes and cardiovascular disease (Raposeiras-Roubín et al. 2010). Although the biomarkers discussed in this chapter thus far were found to be associated with lower baseline lung density and accelerated decline in lung density among smokers, whether the low levels of sRAGE and SP-D are a contributing factor or a consequence of COPD is unclear (Coxson et al. 2013). Circulating sRAGE could be a useful biomarker in monitoring the consequences of novel interventions such as the administration of retinoic acid, stem cell technology, and the use of growth factors targeting the emphysema component of COPD and smoking cessation (Coxson et al. 2013).

Biomarkers in sputum also have been found to change after smoking cessation. In a cross-sectional study of 240 participants, Titz and colleagues (2015) found that the sputum proteome and the transcriptome of former smokers largely approached those in never smokers. Nevertheless, some long-term effects of prior smoking remain evident in the sputum of former smokers, as indicated by the increase in *IFNG* and *NFKB* signaling, which are both associated with an M1 polarization in the sputum of former smokers (Titz et al. 2015). Singh and colleagues (2011) found that IL-18R protein expression was higher on alveolar macrophages in the lung tissue of COPD patients (mean: 23.2%) compared with controls (mean: 2% in former smokers and 2.5% in nonsmokers).

Advances in the Microbiome

The role of the microbiome in COPD pathogenesis has become an active area of research (Martinez et al. 2013; Sze et al. 2014; Mammen and Sethi 2016). Studies have shown that tobacco smoking affects both the oral and intestinal microbiota (Biedermann et al. 2013; Morris et al. 2013), but it is not clear whether the lung microbiota is also affected by tobacco cessation (Morris et al. 2013; Yu et al. 2016). Some researchers postulate that alterations of the gut microbiome may help to explain mechanisms of inflammation in the lung that lead to the development of COPD or its exacerbations (Martinez et al. 2013; Sze et al. 2014; Malhotra and Olsson 2015). Research has revealed that smoking cessation also leads to changes in the microbiome, but it is uncertain whether smoking cessation leads to higher or lower bacterial diversity and whether specific families of bacteria are consistently affected (Delima et al. 2010; Biedermann et al. 2013; Munck et al. 2016; Yu et al. 2016).

Synthesis of the Evidence

Evidence considered in this report strengthens the foundation for inferring that smoking cessation remains the only intervention that attenuates loss of lung function over time among those with COPD and reduces risk of developing COPD in cigarette smokers (USDHHS 1984, 2004, 2014). The beneficial effect of cessation in slowing the decline of lung function in persons with COPD is well documented and was stated in a conclusion of the 1990 Surgeon General's report; the rate of decline decreases after cessation and is maintained at the new lower level unless smoking is resumed (USDHHS 1990). The available evidence shows an immediate benefit over several years for the rate of decline, but does not show whether further gains occur subsequently. Clinical studies show recovery of lung function and improvement in respiratory symptoms shortly after cessation, but inflammation continues to exist months after cessation.

Unfortunately, COPD is a progressive disease in the face of sustained smoking, and at the time of diagnosis the loss of lung function is irreversible. However, further progression can be prevented by cessation. Support for this conclusion, reinforcing that of the 1990 report, comes from the understanding that smoking leads to inflammation and injury of the lungs and from mounting epidemiological evidence that cessation slows the accelerated loss of lung function in smokers. Turning to the criteria used for causal inference in these reports, temporality is appropriate (i.e., cessation is followed by changes in the progression of COPD), the biological basis for a benefit of cessation has been well established in prior Surgeon General's reports, and the epidemiological evidence is consistent.

Further insights on mechanisms are emerging. Recent imaging studies suggest that there are longer-term benefits of cessation (e.g., research has shown measurable reductions in lung density on CT imaging 2 years after cessation). Accordingly, the mechanisms by which smoking cessation attenuates the decline of lung function and reduces the risk of COPD need to be better understood.

Many studies using new approaches are now underway. Studies using biomarkers and omics can provide insights into the potential mechanisms by which smoking cessation could attenuate declines in lung function. This review did not find any evidence to link genetic makeup to how cessation affects this decline. However, studies that evaluated the emerging areas of epigenetics, proteomics, and the microbiome have yielded promising findings.

Conclusions

1. Smoking cessation remains the only established intervention to reduce loss of lung function over time among persons with chronic obstructive pulmonary disease and to reduce the risk of developing chronic obstructive pulmonary disease in cigarette smokers.

2. The evidence is suggestive but not sufficient to infer that airway inflammation in cigarette smokers persists months to years after smoking cessation.

3. The evidence is suggestive but not sufficient to infer that changes in gene methylation and profiles of proteins occur after smoking cessation.

4. The evidence is inadequate to infer the presence or absence of a relationship between smoking cessation and changes in the lung microbiome.

Asthma

Asthma is characterized by variable airflow obstruction, and its symptoms include wheezing and dyspnea with exertion (Chung et al. 2014). Chronic changes in the airway, referred to as airway remodeling, can lead to irreversible loss of lung function (Pascual and Peters 2005). The 2004 and 2014 Surgeon General's reports (USDHHS 2004, 2014) reviewed the topic of active smoking and asthma in children and adults, a topic updated here to focus on smoking cessation. Smoking has detrimental effects on asthma morbidity. Compared with nonsmokers with asthma, smokers with asthma have more severe symptoms, higher rates of hospitalization, accelerated decline in lung function, a shift from eosinophilia toward neutrophilia, and impaired therapeutic response to inhaled and oral corticosteroids (Thomson et al. 2004; McLeish and Zvolensky 2010).

Smoking as a Risk Factor for Asthma

The 2014 Surgeon General's report concluded that the evidence is suggestive but not sufficient to infer a causal relationship between active smoking and the incidence of asthma in adults. With regard to exacerbation of asthma, the report concluded that the evidence is sufficient to infer a causal relationship between active smoking and exacerbation of asthma in adults. In the United States, cigarette smoking is prevalent among persons with asthma. Data from 2010 from the Behavioral Risk Factor Surveillance System show that nearly 17% of people without asthma smoked, and 21% of people with asthma smoked (CDC n.d.). For example, Silverman and colleagues (2003) examined nearly 2,000 persons 18–54 years of age who presented at an emergency department with acute asthma. Asthma symptoms and smoking status were assessed via structured interview. Of persons presenting at the emergency department with acute asthma, 35% were current cigarette smokers, and an additional 23% were former smokers. Interestingly, no difference in pulmonary function was seen between smokers and nonsmokers upon their arrival in the emergency department.

Some observational evidence shows an association between incident asthma and smoking, but the evidence is mixed (McLeish and Zvolensky 2010). The association of smoking with asthma is stronger among certain subgroups of the population. Specifically, among women, the prevalence of asthma is higher among cigarette smokers compared with nonsmokers, but findings have not been consistent in showing a similar difference in the prevalence of asthma among men (McLeish and Zvolensky 2010). Additionally, women who quit smoking may have a higher asthma remission rate (Holm et al. 2007). Most studies concerning adolescents have found higher rates of smoking among adolescents with asthma than among those without asthma (McLeish and Zvolensky 2010). Among adults, this trend is less consistent, possibly because of smoking cessation among adults with asthma.

The U.S. Black Women's Health Study, a prospective cohort study with 46,182 participants, found an exposure-response relationship between smoking and the incidence of adult-onset asthma. Adjusted hazard ratios for former active smoking, current active smoking, and exposure to secondhand smoke were, respectively, 1.36 (95% confidence interval [CI], 1.11–1.67), 1.43 (95% CI, 1.15–1.77), and 1.21 (95% CI, 1.00–1.45) compared with never active or never passive smoking (Coogan et al. 2015). Although current evidence suggests a possible causal relationship between active smoking and the incidence of asthma in adults, the evidence is not sufficient to state conclusively whether smoking is a directly causal risk factor, per the conclusion of the 2014 Surgeon General's report (McLeish and Zvolensky 2010; USDHHS 2014).

Smoking Cessation, Asthma Symptoms, and Lung Function

Asthma-related morbidity and mortality are higher in current cigarette smokers compared with never smokers (Thomson et al. 2004). Smokers with asthma have more severe symptoms (Althuis et al. 1999; Siroux et al. 2000), a greater need for rescue medications (Gallefoss and Bakke 2003), and poorer health status compared with never smokers (Gallefoss and Bakke 2003; Jang et al. 2010). In an experimental study of smokers with asthma, the decrement in FEV_1 after smoking cessation was inversely associated with baseline FEV_1. This finding suggests that

smokers with asthma who have worse lung function may be particularly susceptible to the acute effects of tobacco smoke (Jang et al. 2010). Compared with nonsmokers with asthma, smokers with atopic asthma are less responsive to inhaled adenosine and corticosteroids, which may point toward differences in airway inflammation (Oosterhoff et al. 1993; Lazarus et al. 2007). Admission rates to hospital for asthma and hospital-based care are higher in smokers than in those who have never smoked (Prescott et al. 1997; Sippel et al. 1999), although possibly not in younger adult smokers (Rasmussen et al. 2002). The 6-year mortality rate following a near-fatal asthma attack is higher for smokers than nonsmokers (age-adjusted odds ratio [OR] = 3.6; 95% CI, 2.0–6.2) (Marquette et al. 1992).

In combination, cigarette smoking and asthma accelerate the decline of lung function to a greater degree than either factor alone (Lange et al. 1998; Apostol et al. 2002). For example, the Copenhagen City Heart Study, which included longitudinal measurement of FEV_1 over a 15-year period, found that the average decline in FEV_1 among persons with asthma was greater in smokers than nonsmokers (Lange et al. 1998). The average annual decline in FEV_1 in men with asthma who were 40–59 years of age was 33 mL/year in nonsmokers (n = 36) and 58 mL/year in smokers (n = 150; $p < 0.001$) (Lange et al. 1998). The combination of chronic hypersecretion of mucus and smoking in adults with asthma was associated with a greater decline in FEV_1 than in adults without asthma (Lange et al. 1998). A study of 4,000 adults who were 18–30 years of age at enrollment (Apostol et al. 2002) and who were followed for more than 10 years with serial spirometry measurements found that the decline in FEV_1 was 8.5% in never smokers without asthma (n = 2,393), 10.1% in never smokers with asthma (n = 437), and 11.1% in smokers without asthma (n = 514). The combination of having asthma and smoking ≥15 cigarettes per day (n = 101) had a synergistic effect on the decline in lung function, resulting in a 17.8% decline in FEV_1 over 10 years (Apostol et al. 2002).

Cigarette smoking has been found to decrease the effectiveness of inhaled corticosteroids (Thomson et al. 2004). The mechanisms of corticosteroid resistance in smokers with asthma are not well understood, but this resistance could result from alterations in the phenotypes of airway inflammatory cells (e.g., increased neutrophils, reduced eosinophils); changes in the glucocorticoid receptor α-to-β ratio (e.g., overexpression of glucocorticoid receptor β); and increased activation of proinflammatory transcription factors (e.g., nuclear factor-κB) or reduced activity of histone deacetylase (Thomson et al. 2004). Chalmers and colleagues (2002), who examined the effect of treatment with inhaled fluticasone propionate on morning and evening peak expiratory flow (PEF) among a cohort of steroid-naïve smokers and nonsmokers, found that the mean morning PEF increased significantly more in nonsmokers than in smokers (27 liters [L]/minute vs. -5 L/minute). Inhaled corticosteroids that are often prescribed to treat the exacerbations discussed in this chapter thus far appear to be less effective in treating asthma among smokers (Chalmers et al. 2002). Chaudhuri and colleagues (2006) examined the effects of smoking cessation on lung function and airway inflammation among 32 smokers with asthma at 6 weeks and found a decreased proportion of sputum neutrophils (mean percent difference, 29 [51 to -8]; $p = 0.013$) among those who quit smoking, suggesting a possible mechanism for improved response to inhaled corticosteroids after cessation (Chaudhuri et al. 2006).

Several studies have examined smoking cessation and its association with asthma symptoms and lung function (Table 4.27). For example, Tønnesen and colleagues (2005) examined the effects of smoking cessation and reduction in smoking on asthma symptoms. Participants were divided into three groups: smokers who had reduced their cigarette consumption (to fewer than seven cigarettes per day), former smokers who had achieved complete cessation, and smokers who continued smoking as usual. Participants in both the smoking reduction and smoking cessation groups also used nicotine replacement therapy as an aid to reduce or quit use. Those in the cessation group experienced significant decreases in the use of rescue inhalers, frequency of daytime asthma symptoms, and bronchial hyperreactivity, and they had a 25% reduction in inhaled steroids (Tønnesen et al. 2005). In addition, persons in this group reported significant improvements in both their overall and asthma-related quality of life. Compared with those in the cessation group, improvements were not as great among those who reduced their consumption of cigarettes. Chaudhuri and colleagues (2006) found significant improvements in spirometry (FEV_1 and PEF) among former smokers after 1 week of cessation, and the improvements continued through 6 weeks of cessation. Moreover, asthma control improved, and after 6 weeks of cessation, counts of sputum neutrophils decreased.

Observational studies suggest that cigarette smoking increases the risk for poor asthma control by as much as 175% for such outcomes as asthma attacks, interference with daily activities, and greater severity of wheezing and breathlessness (McLeish and Zvolensky 2010). The wide range of effect sizes appears to be attributable in large measure to differences in methodology across these investigations. Regardless, cigarette smoking among persons with asthma is associated with increased risk of mortality, more frequent asthma attacks, exacerbations of the disease, and symptoms such as wheezing and nighttime awakenings (McLeish and Zvolensky 2010). In persons with asthma, smoking cessation is associated

Table 4.27 Studies on smoking cessation and asthma, 2009–2017

Study	Design/population	Findings
Tønnesen et al. (2005)	• Prospective cohort • 220 smokers with asthma: – 79 reducers (reduced consumption to <7 cigarettes per day) – 82 quitters – 59 continued smokers • Reduction and cessation groups used NRT as cessation aid	Quitters reported a significant decrease in use of rescue inhalers, frequency of daytime asthma symptoms and bronchial hyperactivity, and reduction in inhaled steroid use Those in this group also reported significant improvement both in overall and asthma-related quality of life
Chaudhuri et al. (2006)	• Prospective cohort • 32 smokers with asthma: – 21 quitters – 11 continued smokers • Followed up for 6 weeks • Recorded PEF morning and night	Lung function in quitters improved significantly within a week of stopping smoking and these improvements continued through 6 weeks of cessation
Broekema et al. (2009)	• Cross-sectional • 147 patients with asthma: – 66 never smokers – 46 former smokers – 35 current smokers	Epithelial characteristics in former smokers were similar to those in never smokers, suggesting that smoke-induced changes can be reversed by smoking cessation
Jang et al. (2010)	• Prospective cohort • 22 patients with asthma who continued to smoke • 10 patients with asthma who quit smoking at 3 months • Measured FEV_1	Patients with asthma who quit smoking showed less airway obstruction
Cerveri et al. (2012)	• Prospective cohort • 9,092 with asthma • 1,045 without asthma at 9-year follow-up	Smoking was significantly less frequent among participants with asthma than in the rest of the population (26 vs. 31%; $p < 0.001$)
Polosa et al. (2014)	• Prospective cohort • 18 e-cigarette users with mild-to-moderate asthma • Followed up for 24 months	E-cigarette use ameliorated both objective and subjective asthma outcomes, and beneficial effects may persist in the long term
Munck et al. (2016)	• Prospective cohort • 44 patients with asthma, of whom 25 quit smoking at 12 weeks	Although tobacco smokers with asthma had a greater bacterial diversity in the induced sputum compared with nonsmoking healthy controls, smoking cessation did not change microbial diversity

Notes: **FEV_1 =** forced expiratory volume at 1 second; **PEF =** peak expiratory flow.

with improvements in lung function (specifically PEF), the number of asthma symptoms, treatment outcomes, and asthma-specific quality-of-life scores.

Smoking Cessation Biomarkers and the Microbiome in Asthma

Counts of sputum neutrophils, an indicator of airway inflammation, are reported to be higher in heavy smokers with mild asthma compared with nonsmokers with asthma (Chalmers et al. 2001). Sputum concentrations of cytokines such as IL-8 are also higher in smokers with asthma (Chalmers et al. 2001), but sputum concentrations in other cytokines, such as IL-18, are suppressed in smokers with asthma (McKay et al. 2004). The elevated sputum neutrophil count found in high-intensity smokers with asthma may be partly responsible for their reduced responsiveness to corticosteroids (Meagher et al. 1996). Unlike eosinophils, which are exquisitely sensitive to corticosteroids, neutrophils are poorly responsive to corticosteroid therapy (Green et al. 2002), and their survival and proliferation are promoted by glucocorticoids. In a study of 32 smokers, smoking cessation resulted in reduction in induced sputum neutrophils by bronchoalveolar lavage among subjects with asthma but no change in mediator levels (Chaudhuri et al. 2006). In contrast, research on the effect of smoking cessation on airway inflammation in COPD has shown that elevated levels of most inflammatory cells, including neutrophils, persist in former smokers

(Turato et al. 1995; Domagala-Kulawik et al. 2003; Willemse et al. 2004) and that inflammation can even increase (Willemse et al. 2005). Only a few studies have specifically assessed the lung microbiome among former smokers with asthma (Charlson et al. 2010; Huang et al. 2011; Morris et al. 2013), with Munck and colleagues (2016) finding that current smokers had greater bacterial diversity in their induced sputum and that smoking cessation did not lead to changes in microbial diversity at 12 weeks.

Synthesis of the Evidence

Cigarette smoking has adverse effects on the respiratory health of people with asthma and has been found to causally contribute to the worsening of asthma. Asthma involves chronic inflammation of the airways, and smoking has been shown to increase inflammation, with clinical consequences. Smoking cessation has been linked to improvement in a variety of clinical indicators, including fewer asthma symptoms; less frequent use of inhalers, including inhaled corticosteroids; and improved outcomes, including an attenuation in the decline of lung function, fewer asthma exacerbations, and lower mortality.

In the 2014 Surgeon General's report, the evidence was considered sufficient to infer a causal relationship between active smoking and asthma exacerbations in adults. The report did not specifically address smoking cessation, while offering the recommendation that people with asthma should not smoke, given the causal association of smoking with exacerbations.

The evidence reviewed in this report documents that smoking cessation improves lung function, reduces symptoms, and improves treatment outcomes among persons with asthma. Cohort studies have documented that cigarette smoking acts synergistically with asthma to accelerate the decline of lung function. With regard to the natural history of asthma, the findings of cohort studies also suggest that smoking cessation can attenuate the decline of lung function among persons with asthma (Apostol et al. 2002).

Because smoking is a powerful cause of inflammation of the respiratory tract, cessation would be expected to reduce inflammation in people with asthma, thereby improving clinical status. Thus it is biologically plausible that smoking cessation would improve outcomes in people with asthma who smoke. The observational evidence is consistent with this conclusion but limited in scope, and there are few studies that have followed people with asthma over longer periods of time to characterize how outcomes change with increasing duration of cessation.

Conclusions

1. The evidence is suggestive but not sufficient to infer that smoking cessation reduces asthma symptoms and improves treatment outcomes and asthma-specific quality-of-life scores among persons with asthma who smoke.

2. The evidence is suggestive but not sufficient to infer that smoking cessation improves lung function among persons with asthma who smoke.

Implications

While the evidence remains "suggestive" concerning smoking cessation and clinical outcomes in people with asthma who smoke, clinicians should recommend cessation for their patients with asthma who smoke. Smoking worsens the status of those with asthma, and the evidence reviewed in this report shows favorable consequences of quitting. Even the perception of a causal relationship with asthma among smokers may be an impetus for cessation (Godtfredsen et al. 2001).

Further research is needed to address gaps in the evidence related to smoking cessation and asthma. One area that requires further investigation is the relationship between cigarette smoking and the response to corticosteroids among persons with asthma. The mechanisms for this relationship are not well understood, and smoking cessation studies can help to elucidate pathways and potential therapies, including the potential role of neutrophils in corticosteroid resistance in asthma.

Reproductive Health

The first Surgeon General's report addressed the deleterious effects of maternal smoking on fetal growth (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). Subsequent Surgeon General's reports identified causal associations between active smoking and other adverse reproductive health outcomes for women or men, including decreased female fertility, pregnancy complications, preterm delivery, and erectile dysfunction (U.S. Department of Health and Human Services [USDHHS] 2014). Although the effects of smoking on reproductive health are well established, the benefits of smoking cessation for reproductive health have been studied less extensively. This section provides current information on the potential benefits of smoking cessation

for maternal health during pregnancy, for birth outcomes, and for female and male reproductive health.

Conclusions from Previous Surgeon General's Reports

The 1990 Surgeon General's report on the health benefits of smoking cessation included six conclusions on smoking cessation and reproductive health (Table 4.28) (USDHHS 1990). The report concluded that women who stopped smoking before or during the first trimester of pregnancy had infants with a birth weight similar to that seen among never smoking or nonsmoking women, while smoking cessation later in pregnancy increased infants' birth weights relative to those of infants born to women who continued to smoke throughout pregnancy. In contrast, reductions in smoking intensity during pregnancy did little to reverse the smoking-related reduction of birth weight. The 1990 report also found that women who stopped smoking experienced natural menopause at an age similar to that of nonsmoking women, which was 1 to 2 years later than women who were active smokers.

Four subsequent Surgeon General's reports provided updated conclusions on the reproductive health effects of smoking and the biological mechanisms underlying these effects. However, these reports did not address the effects of smoking cessation (USDHHS 2001, 2004, 2010, 2014).

Literature Review Methods

A systematic literature review was conducted to update the cessation-specific conclusions of the 1990 Surgeon General's report. The search was restricted to English-language articles available on PubMed or EMBASE and published between January 2000 and February 2017. In the PubMed search strategy (Table 4.29), Medical Subject Headings ("MeSH") terms were used to capture relevant articles. Retrieved articles included at least one term related to smoking cessation (e.g., "former smokers") and at least one term related to reproductive health (e.g., "pregnancy"). Citations from retrieved articles and past Surgeon General's reports were used to identify articles not captured by the search, including several articles published between 1997 and 1998.

Sources of Bias in Observational Studies of Smoking and Reproductive Health

Most studies related to prenatal maternal smoking, smoking cessation, and health outcomes rely on self-reports to characterize maternal smoking, but findings from several studies indicate that the use of self-reports to determine smoking status in pregnant women substantially misclassifies exposure as a result of underreporting. For example, various studies that assessed smoking cessation using both self-reports and biochemical markers, such as salivary or urinary cotinine, have found that pregnant women consistently underreport being smokers and generally overreport cessation (George et al. 2006; England et al. 2007; Andersen et al. 2009; Shipton et al. 2009; Dietz et al. 2011; Rode et al. 2013). Notably, in a study of women participating in a randomized trial for preeclampsia prevention, an analysis that included cotinine-validation of self-reported quit status found that the degree of misclassification was lower among women who reported never smoking or who reported quitting before pregnancy than among women who reported quitting after becoming pregnant (England et al. 2007; Rode et al. 2013). In this study, misclassification from over-reporting of cessation led to a modest overestimation of the magnitude of associations between maternal smoking and such outcomes as birth weight and small-for-gestational age (SGA) (England et al. 2007). Finally, reports on quitting late in pregnancy may be subject to more misclassification than reports on quitting early in pregnancy (Tong et al. 2015).

The degree of misclassification of smoking status varies across studies. Factors that may have contributed to this variation include the type of biomarker and the cut point selected for classification of active smoking, the country where the study was conducted, whether women were aware that biochemical validation would occur, when during the pregnancy the women were asked about smoking, the woman's smoking intensity, and the woman's age and other sociodemographic factors. Estimates of the percentage of true active smokers misclassified as quitters or nonsmokers have ranged from 23% to 25% (England et al. 2007; Shipton et al. 2009; Dietz et al. 2011), while estimates of the percentage of self-reported quitters who had evidence from a biomarker of active smoking have ranged from 0% to 25% (George et al. 2006; Andersen et al. 2009; Rode et al. 2013; Tong et al. 2015). Differential misclassification of smoking status by such factors as intensity of smoking can bias the results of studies examining the effects of smoking or smoking cessation on birth outcomes. For example, England and colleagues (2007) found that women who misreported cessation were more likely to be light smokers (1–9 cigarettes per day) than women who accurately reported their smoking status. This misclassification may bias estimates of associations between smoking status during pregnancy and birth outcomes, such as hypertensive disorders of pregnancy and SGA, for both quitters (e.g., by including continuing smokers in the group classified as quitters) and continuing smokers

Table 4.28 Conclusions from the 1990 Surgeon General's report on the health benefits of smoking cessation and reproductive health

Conclusions
1. Women who stop smoking before becoming pregnant have infants of the same birth weight as those born to never smokers.
2. Pregnant smokers who stop smoking at any time up to the 30th week of gestation have infants with higher birth weight than do women who smoke throughout pregnancy. Quitting in the first 3 to 4 months of pregnancy and abstaining throughout the remainder of pregnancy protect the fetus from the adverse effects of smoking on birth weight.
3. Evidence from two intervention trials suggests that reducing daily cigarette consumption without quitting has little or no benefit for birth weight.
4. Recent estimates of the prevalence of smoking during pregnancy, combined with an estimate of the relative risk of low birth weight outcome in smokers, suggest that 17 to 26 percent of low birth weight births could be prevented by eliminating smoking during pregnancy: in groups with a high prevalence of smoking (e.g., women with less than a high school education), 29 to 49 percent of low birth weight births might be prevented by elimination of cigarette smoking during pregnancy.
5. Approximately 30 percent of women who are cigarette smokers quit after recognition of pregnancy, with greater proportions quitting among married women and especially among women with higher levels of educational attainment.
6. Smoking causes women to have natural menopause 1 to 2 years early. Former smokers have an age at natural menopause similar to that of never smokers.

Source: USDHHS (1990, p. 410).

Table 4.29 PubMed systematic search strategy

Smoking search terms	Reproductive health search terms[a]
smoking cessation OR "former smoker" OR "former smokers" OR ex-smok* OR exsmok* OR quit* smok* OR stop* smok*	reproduction OR reproductive OR Reproductive Health[mh] OR Reproductive Medicine[mh] OR birth OR Parturition[mh] OR pregnancy OR pregnan* OR gestation* OR fertility OR infertility OR fertile OR infertile OR fecundability OR fecundity OR subfertility OR "sub-fertility" OR Subfertile OR "sub-fertile" OR amenorrhea OR conception OR Fertilization[mh] OR "spontaneous abortion" OR "Abortion, Spontaneous"[mh] OR stillbirth OR Miscarriage* OR Fetal Death[mh] OR preterm OR Premature Birth[mh] OR "Infant, Premature"[mh] OR "Obstetric Labor, Premature"[mh] OR placenta OR Placenta Diseases[mh] OR preeclampsia OR "Pre-Eclampsia"[mh] OR "pre-eclampsia" OR "fetal growth" OR Fetal Development[mh] OR Fetal Growth Retardation[mh] OR birthweight OR "birth weight" OR "Infant, Low Birth Weight"[mh] OR Birth Weight[mh] OR "fetal mortality" OR Fetal Mortality[mh] OR "neonatal mortality" OR "perinatal mortality" OR Perinatal Mortality[mh] OR Perinatal Death[mh] OR "infant mortality" OR Infant Mortality[mh] OR congenital OR Congenital Abnormalities[mh] OR SIDS OR Sudden Infant Death[mh] OR "Sudden Infant Death" OR menopause OR "sexual performance" OR "sexual dysfunction" OR "Sexual Dysfunction, Physiological"[mh] OR erection OR Penile Erection[mh] OR erectile OR Erectile Dysfunction[mh] OR impotence OR "Impotence, Vasculogenic"[mh] OR sperm OR Spermatozoa[mh] OR Spermatogenesis[mh] OR semen OR Semen Analysis[mh] OR Prenatal OR "pre-natal" OR Prenatal Care[mh] OR Prenatal Injuries[mh] OR Prenatal Diagnosis[mh] OR "Embryonic and Fetal Development"[mh]

Notes: **Mh =** to search Medical Subjects Headings (MeSH) in MEDLINE or PubMed.
[a]Used in conjunction with all smoking search terms.

(e.g., by omitting light smokers because they incorrectly reported cessation) (England et al. 2007).

Many studies of the association of tobacco use with pregnancy outcomes have assessed smoking status at a single point during pregnancy, but because women may change their patterns of tobacco use during pregnancy by quitting, cutting back, and/or relapsing, using a single assessment of exposure can result in misclassification of exposure across a pregnancy (Pickett et al. 2003, 2005). For example, in a prospective cohort of Dutch women, 34% reported cessation during the first trimester, but were later reclassified as continuing smokers after responding to questionnaires in the second and third trimesters (Bakker et al. 2011). Thus the assessment of

smoking status at a single time point rather than multiple time points during pregnancy can result in misclassification of exposure (Pickett et al. 2009).

Overall, women who smoke differ from those who do not in several ways with regard to lifestyle and behaviors, leading to the potential for confounding (Subar et al. 1990; Midgette et al. 1993; Maxson et al. 2012). For example, smokers may be more likely than nonsmokers to use alcohol and/or illicit substances that can affect birth outcomes (Coleman-Cowger et al. 2017). Fully controlling for these differences in estimating the benefits of quitting can be difficult, but failure to do so may result in unrecognized residual confounding, which was illustrated, for example, in a study of Swedish women. There, Juárez and Merlo (2013) compared results of a conventional multivariable linear regression analysis with those of a multilevel analysis that used siblings to estimate woman-specific, smoking-associated changes in birth weight (i.e., comparing the birth weights of infants born to the same woman whose exposure to smoking changed between pregnancies and controlling for birth order). The association between maternal smoking behavior and birth weight remained significant in the sibling analysis, but it was attenuated in comparison with the conventional analysis. Specifically, the babies of women who smoked heavily throughout pregnancy had an adjusted reduction in birth weight of 303 grams (g) relative to those of nonsmokers in the conventional analysis; in the sibling analysis, the reduction was 226 g. Using similar methods in a cohort of Danish births, Obel and colleagues (2016) also found that the association between smoking during pregnancy and low birth weight (<2,500 g) was moderately attenuated in a sibling analysis in comparison with a conventional analysis (adjusted odds ratio [aOR] = 1.68 and 2.60, respectively).

Pregnancy Complications

Ectopic Pregnancy

An ectopic pregnancy, which occurs when implantation of the fertilized ovum takes place outside the uterus, most often in the fallopian tubes, affects an estimated 1% to 2% of pregnancies (CDC 1995; Van Den Eeden et al. 2005). The 1990 Surgeon General's report found only sparse evidence that current or former smokers were at higher risk of ectopic pregnancy (Chow et al. 1988; USDHHS 1990; Kalandidi et al. 1991; Stergachis et al. 1991; Parazzini et al. 1992; Phillips et al. 1992; Saraiya et al. 1998; Bouyer et al. 2003; Karaer et al. 2006), but the 2014 Surgeon General's report found sufficient evidence to conclude that active smoking causally increases the risk of ectopic pregnancy (USDHHS 2014). Potential mechanisms underlying this relationship identified from animal research include damage to a fallopian tube or dysfunction of that structure, damage to the oviduct epithelium, a decrease in the ratio of ciliated to secretory oviductal cells, a decrease in smooth muscle contractions of the oviduct, and decreased oviductal blood flow (USDHHS 2014). A review of studies that included former smokers with an ectopic pregnancy found that the majority of studies reported no significant association between that outcome and past smoking (Chow et al. 1988; Kalandidi et al. 1991; Stergachis et al. 1991; Parazzini et al. 1992; Phillips et al. 1992; Saraiya et al. 1998; Bouyer et al. 2003; Karaer et al. 2006).

Summary of the Evidence

The 2014 Surgeon General's report concluded that "the evidence is sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy" (USDHHS 2014, p. 487). A systematic review of the literature did not identify additional studies since that report that assessed the risk of ectopic pregnancy among former smokers. Therefore, a new conclusion on smoking cessation and ectopic pregnancy is not provided in this report.

Spontaneous Abortion

Spontaneous abortion is defined as the involuntary termination of an intrauterine pregnancy before 20 weeks' gestation, although it is sometimes defined as occurring before 28 weeks. Recognized spontaneous abortion occurs in approximately 12% of pregnancies, usually before 12 weeks' gestation (McNair and Altman 2011). Very early losses may go unrecognized, and the true incidence of pregnancy loss may be as high as 30% to 45% (Wilcox et al. 1988; Eskenazi et al. 1995).

The 1990 Surgeon General's report did not provide a conclusion about the association between smoking cessation and spontaneous abortion because of a paucity of research among former smokers. The 2004 Surgeon General's report, however, reviewed the evidence on an association between maternal smoking and spontaneous abortion, finding the evidence suggestive but not sufficient to infer a causal relationship (USDHHS 2004), and cessation was not examined. The 2010 Surgeon General's report updated the 2004 report, but it did not include conclusions on the strength of evidence for causality. Proposed mechanisms underlying a potential association that were set forth in that report included effects of hypoxia due to exposure to CO, vasoconstrictive and antimetabolic effects resulting from placental insufficiency, and the direct toxic effects of constituents in cigarette smoke (USDHHS 2010). The 2014 Surgeon General's report noted that

studies have found associations between active smoking and spontaneous abortion, but it considered the evidence suggestive but not sufficient to reach a causal conclusion, in part because of study limitations, including difficulty controlling for potential confounders and a lack of data on conception karyotype (USDHHS 2014).

Summary of the Evidence

The 2014 Surgeon General's report concluded that "the evidence is suggestive, but not sufficient, to infer a causal relationship between maternal active smoking and spontaneous abortion" (USDHHS 2014, p. 489). However, a systematic review of the literature identified no known studies that have specifically assessed the association between smoking cessation and risk of spontaneous abortion; therefore, this report does not make any new conclusions regarding this outcome.

Placental Abruption

Placental abruption, which affects an estimated 0.3% to 2% of pregnancies (Ananth et al. 2015; Ruiter et al. 2015), is the premature separation of the placenta from the uterine wall (Rasmussen et al. 1996; Ananth et al. 2001, 2005; Kyrklund-Blomberg et al. 2001; Luke et al. 2017; Räisänen et al. 2018). Placental abruption can lead to perinatal mortality (Raymond and Mills 1993; Ananth and Wilcox 2001; Kyrklund-Blomberg et al. 2001; Räisänen et al. 2018), neonatal asphyxia (Heinonen and Saarikoski 2001), preterm delivery, significant maternal blood loss, and disseminated intravascular coagulation (Hladky et al. 2002).

The only study on the risk of placental abruption (Naeye 1980) cited in the 1990 Surgeon General's report (USDHHS 1990) found that smoking for more than 6 years was associated with an increased risk of placental abruption, but that women who quit smoking by their first prenatal visit were not at increased risk of placental abruption relative to never smokers. The 2004 Surgeon General's report found sufficient evidence to conclude that maternal smoking increases the risk of placental abruption, and it included one study demonstrating increased risk of this event in former smokers (Spinillo et al. 1994; USDHHS 2004). That study, however, was limited by its small sample, and it did not include information about the timing of cessation. The 2010 Surgeon General's report reviewed potential mechanisms underlying the association between smoking and abruption, including smoking-related degenerative and/or inflammatory changes in the placenta, reduced vitamin C levels and impaired collagen synthesis in smokers, microinfarcts, and atheromatous changes in placental vessels (USDHHS 2010). That report identified one study indicating that, when women stop smoking between pregnancies, their risk of abruption is similar to that of nonsmokers (Ananth and Cnattingius 2007). Because abruption is a rare outcome, large, population-based samples are needed to study risk factors for its occurrence. One study published since the 2010 report (Räisänen et al. 2014) had a sufficient sample to examine smoking cessation and placental abruption. In this population-based cohort of more than 1 million births in Finland, Räisänen and colleagues (2014) found that placental abruption occurred in 0.3% of pregnancies among both nonsmokers and women who quit smoking during the first trimester of pregnancy, but in 0.6% of pregnancies among women who continued to smoke after the first trimester. That study, however, did not include adjustments for covariates, and the results of testing for statistical significance were not presented. A smaller study of births at an Australian hospital found that women who were smokers at the first antenatal visit did not differ significantly in risk of placental abruption from nonsmokers (aOR = 0.82; 95% confidence interval [CI], 0.27–2.44) or from women who quit smoking within a year before their first antenatal visit (aOR = 2.45; 95% CI, 0.20–29.29) (Bickerstaff et al. 2012).

Summary of the Evidence

The 2004 Surgeon General's report found sufficient evidence to conclude that maternal smoking increases the risk of placental abruption. Since then, only two studies have examined smoking cessation and risk of placental abruption, and both had important methodological limitations. Consequently, the evidence is inadequate to infer that smoking cessation before or during early pregnancy reduces the risk of placental abruption compared with continued smoking.

Placenta Previa

Placenta previa is the complete or partial obstruction of the cervix by the placenta, a problem that affects an estimated 0.4% to 0.7% of births (Comeau et al. 1983; Iyasu et al. 1993; Faiz and Ananth 2003; Luke et al. 2017). Placenta previa can lead to important maternal and infant complications, including preterm delivery, hemorrhage, and even maternal, fetal, or neonatal death (Salihu et al. 2003; Creasy et al. 2004). One mechanism through which smoking could increase risk for this condition is compensatory placental enlargement in response to chronic hypoxia and ischemia resulting from smoking (USDHHS 2010).

The 1990 Surgeon General's report cited only one study examining the risk of placenta previa among former smokers (Naeye 1980); this study found that women who quit smoking before or during early pregnancy were

at increased risk relative to never smokers. The 2004 Surgeon General's report found sufficient evidence to conclude that active smoking increases the risk of placenta previa, but it did not address risk in former smokers (USDHHS 2004). Since the 2004 report, two studies have examined placenta previa in quitters. In a study of Finnish women, Räisänen and colleagues (2014) observed that placenta previa occurred in an estimated 0.2% of pregnancies in each of four exposure groups (nonsmokers, women who quit smoking during the first trimester, women who continued to smoke after the first trimester, and women for whom no information was available on their smoking status). As indicated earlier, however, the study did not adjust for covariates, and the results of testing for significance were not presented. In their study of Australian women, Bickerstaff and colleagues (2012) found that women who had quit smoking in the 12 months before entry into prenatal care had a reduced risk of placenta previa compared with those still smoking when they entered prenatal care, but the difference was not statistically significant (aOR = 0.45; 95% CI, 0.16–1.29).

Summary of the Evidence

Since the 2004 Surgeon General's report, only two studies have examined smoking cessation and risk of placental abruption, and both had important methodological limitations. Consequently, the evidence is inadequate to determine whether smoking cessation before or during pregnancy reduces the risk of placenta previa compared with continued smoking.

Premature Rupture of Membranes

Premature rupture of the membranes (PROM) refers to rupture of the amniotic sac before the onset of labor. When this occurs before 37 weeks' gestation, it is referred to as preterm PROM (PPROM). PPROM complicates 1–2% of pregnancies, and it may contribute to up to 40% of preterm deliveries (Arias and Tomich 1982; Mercer et al. 2000; Lee and Silver 2001; Bond et al. 2017; Mercer 2017). PPROM (Smith et al. 2005) increases perinatal morbidity and mortality through increased rates of preterm delivery and by elevating the risk of intra-amniotic infection, neonatal sepsis, placental abruption, and pulmonary hypoplasia (Bond et al. 2017; Sim et al. 2017). Risk factors for PPROM include nutritional deficiencies in vitamin C (Hadley et al. 1990; Casanueva et al. 1993; Woods Jr et al. 2001; Siega-Riz et al. 2003), copper (Artal et al. 1979; Kiilholma et al. 1984), and zinc (Sikorski et al. 1988; Harger et al. 1990; Ekwo et al. 1992; Scholl et al. 1993); vaginal bleeding (Harger et al. 1990; Ekwo et al. 1992; Committee on Practice Bulletins—Obstetrics 2016); bacterial vaginosis (Kurki et al. 1992; Mercer et al. 2000); and intra-amniotic infections (Naeye and Peters 1980; Ekwo et al. 1993; Heffner et al. 1993; Asrat 2001; Committee on Practice Bulletins—Obstetrics 2016). PROM may result from structural deficiencies of the chorioamniotic membranes (Lee and Silver 2001; Tchirikov et al. 2018), disruptions in collagen metabolism (Draper et al. 1995; Tchirikov et al. 2018), and accelerated senescence of membranes because of high levels of oxidative stress (Menon et al. 2014).

The 1990 Surgeon General's report on smoking cessation did not consider associations between cessation and PROM. The 2004 Surgeon General's report on smoking concluded that active smoking causally increases the risk of PROM (USDHHS 2004). Hypothesized mechanisms included effects of smoking on the immune system, resulting in increased risk of genital tract infections or inflammatory responses or reductions in nutrients, such as vitamin C (USDHHS 2010). One study included in the 2004 report assessed risk in former smokers; the aOR for PPROM among quitters compared with never smokers was less than that for continuing smokers versus never smokers (aOR = 1.58; 95% CI, 0.77–3.27 and aOR = 2.08; 95% CI, 1.37–3.13, respectively), suggesting that smoking cessation may reduce the risk of PPROM compared with continued smoking (Harger et al. 1990).

Four studies published since the 2004 Surgeon General's report have examined the risk of PROM and/or of PPROM in smokers and quitters. Bickerstaff and colleagues (2012) found that the risk of term PROM in women who had quit smoking in the 12 months before entry into prenatal care did not differ significantly from that of women still smoking when they entered prenatal care (aOR = 0.61; 95% CI, 0.33–1.15). Later, Blatt and colleagues (2015) analyzed data from certificates of live births in Ohio and found that women who quit after the second trimester had a higher incidence of PROM (5.3%) than nonsmokers and continuing smokers (2.8% and 3.2%, respectively), but they did not report results of testing for statistical significance or adjustments for confounders. In a subsample of women in this cohort with a previous preterm delivery, Wallace and colleagues (2017) found that second-trimester quitters also experienced the highest prevalence of PROM (14.4%), with rates of 6.2% and 7.3% for nonsmokers and continuing smokers, respectively. Again, potential confounding was not addressed, and it is possible that the findings could be explained by reverse causation (i.e., the occurrence of pregnancy complications could have motivated late-pregnancy cessation). Finally, in a study involving data from three randomized trials of metronidazole for bacterial vaginosis that included more than 4,000 deliveries, Andres and colleagues (2013) found no differences in risk of PPROM between nonsmokers (4.1%), smokers who

quit during pregnancy (4.2%), and continuing smokers (4.5%); the OR for quitters was 1.04 (95% CI, 0.55–1.95) in a comparison with nonsmokers. Adjustment for demographic and obstetrical factors did not change this finding.

Summary of the Evidence

The 2004 Surgeon General's report found sufficient evidence to conclude that maternal smoking increases the risk of PROM (USDHHS 2004). Since then, studies examining the effect of smoking cessation compared with continuing to smoke on the risk of PROM have not shown significant reductions in risk, and in one sample from Ohio, PROM risk appears to have increased in quitters. Therefore, the evidence is inadequate to determine whether smoking cessation before or during pregnancy reduces the risk of PROM compared with continuing to smoke.

Preeclampsia

Preeclampsia is a syndrome of reduced organ perfusion attributable to vasospasm and endothelial activation that is marked by proteinuria, hypertension, and dysfunction of the endothelial cells lining the uterus, with onset after 20 weeks' gestation. Eclampsia refers to a condition in which preeclampsia is accompanied by generalized seizures not explained by other causes (Cunningham et al. 2013). Preeclampsia affects an estimated 1% to 6% of pregnancies (Abalos et al. 2013). Advances in research during the past 15 years have led to significant progress in our understanding of the etiology of preeclampsia. A process known as pseudo-vascularization enables increased uteroplacental perfusion and adequate oxygen and nutrient transport to the fetus by converting low-capacity uterine spiral arteries into high-capacitance, low-resistance vessels; this requires the upregulation of proangiogenic molecules in processes completed by around 20 weeks' gestation. Evidence indicates that preeclampsia is a manifestation of an imbalance between proangiogenic factors, such as placental growth factor (PlGF), and antiangiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng). Elevated levels of sFlt-1 and reduced levels of PlGF have been documented in women with preeclampsia, and evidence of this imbalance can precede the onset of clinical disease (Chaiworapongsa et al. 2004; Levine et al. 2004; Robinson et al. 2006). Importantly, pseudo-vascularization is incomplete in preeclampsia; cytotrophoblasts do not adequately invade the spiral arteries, resulting in placental ischemia, downregulation of proangiogenic vascular endothelial growth factor (VEGF) family molecules, and upregulation of antiangiogenic placental factors, such as sFlt-1 and sEng. The etiology of abnormal placentation that precedes preeclampsia is uncertain, but it may involve placental hypoxia, oxidative stress, and genetic factors (Jim and Karumanchi 2017).

An inverse association between maternal cigarette smoking and the risk of preeclampsia has been recognized for decades, and now some mechanistic understanding exists of this association. Smoking during pregnancy has been associated with reduced sFlt-1 levels in uncomplicated pregnancies (Levine et al. 2006; Jeyabalan et al. 2008), and a reduction in the ratio of sFlt-1:PlGF has been described in smokers with preeclampsia (Jääskeläinen et al. 2017). Notably, reductions in the risk of preeclampsia have not been observed in users of smokeless tobacco, suggesting that nicotine is not the agent responsible for reduced risk in cigarette smokers. In an sFlt-1 preeclampsia-like mouse model, treatment with low-dose CO prevented late-gestation hypertension, proteinuria, and reduced Bowman's space in the kidneys (Venditti et al. 2014), supporting a role for CO rather than nicotine.

Some investigators have proposed that preeclampsia is a two-stage disease, requiring abnormal placentation, insufficient invasion of extravillous cytotrophoblasts, insufficient remodeling of the maternal spiral arteries, and reduced placental perfusion in the first stage, followed by the clinical stages of the disease that involve the release of damaging endothelial factors into the maternal circulation (Roberts and Hubel 2009; Palei et al. 2013; Gathiram and Moodley 2016). It is unclear whether smoking could affect the risk of preeclampsia in one or both of these stages. Developing a better understanding of the implications of the timing of exposure to cigarette smoking in the risk of preeclampsia could lead to a better understanding of the underlying pathophysiological process and point to potential treatments.

The 1990 Surgeon General's report found that the available data supported the idea that former smokers were at reduced risk of preeclampsia relative to never smokers (although to a lesser extent than active smokers) (Marcoux et al. 1989; USDHHS 1990), but there was inadequate evidence from which to draw causal conclusions (USDHHS 1990). The 2004 Surgeon General's report concluded that maternal active smoking is causally associated with reduced risk of preeclampsia, but it did not review the outcomes with regard to former smokers (USDHHS 2004). The 2010 and 2014 reports reviewed potential underlying mechanisms (summarized above), but they did not review the outcomes for risk relative to smoking cessation.

A 2007 review of preeclampsia and smoking included six studies of the risk of preeclampsia in quitters (England and Zhang 2007); of the three studies that evaluated risk in women who quit before pregnancy, none found a significant protective effect among quitters (Marcoux et al.

1989; England et al. 2002; Parazzini et al. 2003). Four of the six studies examined cessation during pregnancy: one found a significantly reduced risk in quitters (Sibai et al. 1995), and three reported point estimates less than unity but no statistically significant associations (Marcoux et al. 1989; Martin et al. 2000; England et al. 2002). Finally, one study combined women who quit before pregnancy with women who quit during early pregnancy and reported no significant associations for any intensity of smoking (Zhang et al. 1999).

Table 4.30 presents eight studies published in 2007 or later and not included in the above review that assessed the relationship between smoking status (including cessation) and risk of preeclampsia. One of the eight (England et al. 2007) was a reanalysis of an earlier study (England et al. 2002) that was included in the review by England and Zhang (2007), but in the reanalysis, the authors used urine cotinine to validate cessation. Two of the eight studies combined preeclampsia with gestational hypertension and thus did not evaluate preeclampsia separately (England et al. 2007; Blatt et al. 2015); two assessed cessation before pregnancy (Blatt et al. 2015; Kharkova et al. 2017); one combined cessation before pregnancy with cessation during early pregnancy (England et al. 2007); and six assessed cessation during pregnancy (Fasting et al. 2009; Xiong et al. 2009; Wikstrom et al. 2010; Engel et al. 2013; Räisänen et al. 2014; Blatt et al. 2015). Five of the eight studies reported results of statistical testing, and none found a significant reduction in the risk of preeclampsia among quitters. Two of the three studies not reporting results of statistical testing reported prevalence estimates in quitters that were lower than those in nonsmokers (Räisänen et al. 2014; Blatt et al. 2015), but in one study, this was only true for women who quit in the second trimester (Blatt et al. 2015), and neither of these studies adjusted for potential confounders (preeclampsia was not a primary outcome in either study). Of the six studies assessing cessation during pregnancy, the timing of cessation varied, including at greater than 28 weeks gestation (Fasting et al. 2009), in the first 20 weeks gestation or the second 20 weeks gestation (Xiong et al. 2009), between 15 and 30 weeks gestation (Wikstrom et al. 2010), in the first trimester or in the second trimester (Engel et al. 2013), and in the first trimester (Räisänen et al. 2014; Blatt et al. 2015).

All eight studies found lower point estimates for risk of preeclampsia among women who continued to smoke during pregnancy compared with women who did not smoke (range of aORs = 0.5–0.8) (England et al. 2007; Fasting et al. 2009; Xiong et al. 2009; Wikstrom et al. 2010; Engel et al. 2013; Räisänen et al. 2014; Blatt et al. 2015; Kharkova et al. 2017). Findings were statistically significant in four studies (England et al. 2007; Wikstrom et al. 2010; Engel et al. 2013; Kharkova et al. 2017) and not significant in one study (Xiong et al. 2009), and the results of statistical testing were not presented in three studies (Fasting et al. 2009; Räisänen et al. 2014; Blatt et al. 2015). Of interest, one of the three studies with a significant finding was a large population-based study in Sweden in which women who did not smoke at the first antenatal visit, but who had resumed by the third trimester, had a significantly reduced risk of preeclampsia compared with women who did not smoke during pregnancy (aOR = 0.65; 95% CI, 0.50–0.85) (Wikstrom et al. 2010).

Summary of the Evidence

The 2004 Surgeon General's report concluded that maternal active smoking is causally associated with reduced risk of preeclampsia (USDHHS 2004). Results of studies published since the 2004 report provide additional support that continued smoking during pregnancy is associated with reduced risk of preeclampsia. However, the review did not find substantial evidence to support an inverse association between smoking before or during early pregnancy and reduced risk of preeclampsia among women who quit smoking before late pregnancy. Therefore, the evidence is insufficient to conclude that smoking during early or mid-pregnancy alone, and not during late pregnancy, is associated with a reduced risk of preeclampsia. Continued smoking may reduce the risk of preeclampsia through its effects on angiogenic factors late in pregnancy rather than through upstream effects on placentation during early pregnancy, but the evidence is currently insufficient to draw conclusions about such mechanisms.

Gestational Weight Gain

Weight gain associated with smoking cessation has been well described in the general population (reviewed by Bush et al. 2016), but it has been less well studied in pregnant and postpartum women. Fear of weight gain and/or weight retention could be a barrier to cessation or sustained abstinence from smoking in pregnant and postpartum women (Lawson 1994; Hotham et al. 2002; Berg et al. 2008). Gaining weight above the recommended levels (Institute of Medicine [IOM] 2009) can result in infants' being born large for gestational age (Goldstein et al. 2017), and weight gain below the recommended levels can result in infants' being born small for gestational age or with low birth weight (Siega-Riz et al. 2009). Smoking cessation during pregnancy could have unintended adverse effects on pregnancy or other health outcomes by increasing the number of pregnancies with excessive weight gain; conversely, smoking cessation-related weight gain could also reduce the number of pregnancies with inadequate weight

Table 4.30 Studies on smoking cessation and preeclampsia

Study	Design	Tobacco exposure	Outcome definition	Outcomes/findings	Comments
England et al. (2002) (original analysis); England et al. (2007) (reanalysis)	• Randomized trial for preeclampsia prevention (2007 study was a reanalysis of 2002 study) • n = 4289 • 1992–1995 • United States (multisite)	• Nonsmokers: Never smoked regularly • Quit before pregnancy: Quit before last menstrual period, validated with cotinine mid-pregnancy • Quit during pregnancy: Quit after last menstrual period, validated with cotinine mid-pregnancy • Continued smoking: Smoking at study enrollment • Smoking status based on self-reports obtained at study enrollment (13–21 weeks' gestation) in 2007 study • Quit status validated with urine cotinine concentration obtained mid-pregnancy (mean: 28 weeks) • For 2007 analysis, quit groups were combined	**2002 analysis**: • Preeclampsia: Gestational hypertension plus proteinuria within 7 days or the development of HELLP syndrome or eclampsia in the presence of hypertension **2007 analysis**: • Hypertensive disorders of pregnancy: Pregnancy-associated hypertension without proteinuria, preeclampsia, or eclampsia	**2002 analysis—adjusted RR for preeclampsia (95% CI):** • Quit before pregnancy: 1.1 (0.7–1.7) • Quit during pregnancy: 0.9 (0.6–1.3) • Continued smoking: 0.7 (0.5–1.1) **2007 reanalysis—crude and adjusted OR for hypertensive disorders of pregnancy (95% CI):** • Quit preconception or by mid-pregnancy: – Unadjusted: 0.9 (0.8–1.2) – Adjusted: 1.1 (0.9–1.3) • Continued smoking: – Unadjusted: 0.6 (0.5–0.7) – Adjusted 0.6 (0.5–0.8)	Reanalysis of data used in 2002 study after obtaining cotinine validation of smoking status Results adjusted for maternal BMI, study center, and private health insurance Did not account for alcohol or substance use
Fasting et al. (2009)	• Prospective intervention study to prevent allergies in children • n = 711 • 2000–2002 • Norway	• Nonsmoker: Not smoking when became pregnant • Quit smoking: Smoking when became pregnant, quit by study enrollment • Continued smoking: Smoking when became pregnant, still smoking at enrollment • Smoking status based on self-reports collected at enrollment (median gestational age: 11 weeks, all <28 weeks)	Preeclampsia assessed by maternal questionnaire	**Number (%) of women with preeclampsia** • Nonsmoker: 21 (4%) • Quit smoking: 11 (10%) • Continued smoking: 1 (2%)	Results not adjusted for potential confounders Results of statistical testing not presented Did not account for alcohol or substance use

Table 4.30 Continued

Study	Design	Tobacco exposure	Outcome definition	Outcomes/findings	Comments
Xiong et al. (2009)	• Case-control study • n = 337 • 2003–2006 • Quebec, Canada	• Nonsmokers: Did not smoke before or during pregnancy • Quit smoking early: Smoked during pregnancy but quit in the first 20 weeks • Quit smoking late: Smoked during pregnancy but quit in the second 20 weeks of pregnancy • Continued smoking: Smoked before and during pregnancy • Smoking status based on self-reports ascertained from interviews conducted during postpartum period	Preeclampsia: Blood pressure at least 140/90 on two occasions at least 4 hours apart after 20 weeks' gestation and with proteinuria	**Unadjusted and adjusted OR for preeclampsia (95% CI):** • Nonsmokers: Reference • Quit smoking early: – Unadjusted: 0.91 (0.42–1.96) – Adjusted 1.03 (0.41–2.60) • Quit smoking late: – Unadjusted: 0.79 (0.21–2.96) – Adjusted 0.78 (0.12–5.02) • Continued smoking: – Unadjusted: 0.63 (0.23–1.73) – Adjusted 0.62 (0.16–2.37)	Results adjusted for maternal age, race, education, marital status, family income, BMI, gravidity, abortion, alcohol consumption, and cesarean section Did not account for alcohol or substance use
Wikström et al. (2010)	• Population-based cohort study • Swedish Medical Birth Register • Singleton, term births • n = 379,214 • 1999–2006 • Swede	• Nonuser: Did not smoke or use tobacco at either study visit (early or late) • Quit by late pregnancy: Smoked at the early visit but not the late visit • Continued smoking: Smoked at the time of both visits (early and late) • Started smoking by late pregnancy: Did not smoke at early visit but smoked at late visit • Smoking status obtained by midwives from maternal self-reports at entry into prenatal care (<15 weeks' gestation) and at 30–32 weeks' gestation	Preeclampsia identified using ICD-10 codes Blood pressure ≥140/90 with proteinuria after 20 weeks' gestation	**Adjusted OR for preeclampsia**: • Nonsmoker: Reference • Quit by late pregnancy: 0.94 (0.83–1.08) • Continued smoking: 0.50 (0.45–0.56) • Started smoking by late pregnancy: 0.65 (0.50–0.85)	Results adjusted for early-pregnancy BMI, maternal age, parity, and years of education Did not account for substance use
Engel et al. (2013)	• Population-based prospective cohort • n = 70,729 • 1999–2008 • Norway	• Nonsmoker: Never smoked • Smoked first trimester only • Smoked first and second trimesters • Smoked first and third trimesters • Smoked third trimester only • Smoked all trimesters • Smoking status obtained from maternal interviews conducted in early pregnancy (~18 weeks) and late pregnancy • (~30 weeks)	Preeclampsia obtained from registry, diagnosis obtained by midwife from antenatal medical record	**Adjusted OR for preeclampsia (95% CI):** • Nonsmoker: Reference • Smoked first trimester only: 0.99 (0.87–1.11) • Smoked first and second trimesters: 0.89 (0.64–1.23) • Smoked first and third trimesters: 0.62 (0.31–1.27) • Smoked third trimester only: 0.78 (0.20–3.09) • Smoked all trimesters: 0.57 (0.46–0.70)	Results adjusted for parity, maternal education, BMI, education level, diabetes, and multiple observations per woman Did not account for alcohol or substance use

Table 4.30 Continued

Study	Design	Tobacco exposure	Outcome definition	Outcomes/findings	Comments
Räisänen et al (2014)	• Population based retrospective cohort • Finnish Medical Birth Register • Singleton deliveries, live or stillborn after 22 weeks' gestation • n = 1,164,953 • 1991–2010 • Finland	• Nonsmokers • Quit smoking: Quit during the first trimester • Continued smoking: Still smoking after the first trimester • Smoking history based on self-reports ascertained from the Finnish Medical Birth Register • Details on when and how data were collected were not reported	Preeclampsia definition and ascertainment not described	**Percentage preeclampsia**: • Nonsmokers: 2.0% • Quit smoking: 1.1% • Continued smoking: 1.3%	Results not adjusted for potential confounders Results of statistical testing not presented Did not account for alcohol or substance use
Blatt et al. (2015)	• Population-based retrospective cohort • Ohio certificates of live birth • n = 927,424 • 2006–2012 • Ohio	• Nonsmoker: Did not smoke during the 3 months before pregnancy or during pregnancy • Quit preconception: Smoked during the 3 months before pregnancy but not during pregnancy • Quit first trimester: Smoked first trimester only • Quit second trimester: Smoked first and second trimester, not third • Continued smoking: Smoked throughout pregnancy • Smoking history ascertained from vital statistics data and certificates of live birth	Gestational hypertension/ preeclampsia combined; obtained from certificate of live birth	**Percentage gestational hypertension/ preeclampsia:** • Nonsmokers: 4.6% • Quit preconception: 5.2% • Quit first trimester: 4.9% • Quit second trimester: 4.2% • Continued smoking: 3.3%	Findings not adjusted for potential confounders Results of statistical testing not presented Did not account for alcohol or substance use
Kharkova et al. (2017)	• Population-based study using registry data • n =39,566 • 2006–2009 • Russia	• Nonsmokers: Did not smoke before or during pregnancy • Quit smoking: Smoked before but not during pregnancy • Continued smoking: Smoked before and during pregnancy • Smoking status based on self-reports obtained at first antenatal visit	Preeclampsia or eclampsia classified according to ICD-10 definitions: hypertension ≥140/90 accompanied by edema and proteinuria with onset after 20 weeks' gestation; eclampsia was convulsions or coma in pregnant or puerperal women with hypertension, edema, or proteinuria	**OR for eclampsia/preeclampsia:** • Smokers: Reference • Quit smoking: – Unadjusted: 1.09 (0.91–1.30) – Adjusted: 1.10 (0.91–1.32) • Nonsmokers: – Unadjusted: 1.32 (1.19–1.47) – Adjusted: 1.37 (1.23–1.54)	Results adjusted for maternal age, residence, ethnicity, marital status, parity, alcohol abuse, year of delivery, BMI, and excessive weight gain Did not account for substance use

Notes: **BMI =** body mass index; **CI =** confidence interval; **kg =** kilogram; **ICD =** International Classification of Diseases; **lbs =** pounds; **HELLP =** hemolysis, elevated liver enzymes, and low platelet count; **OR =** odds ratio; **RR =** risk ratio: **SD =** standard deviation.

gain. In 2015, 48% of U.S. women gained weight in excess of recommended levels, and 21% gained below recommended levels (CDC 2016b).

The 1990 Surgeon General's report noted that, compared with continued smoking, cessation during pregnancy may be associated with increased gestational weight gain (USDHHS 1990). More recent Surgeon General's reports have not addressed gestational weight gain and smoking cessation.

In a 2017 Cochrane Review of psychosocial interventions for supporting women to stop smoking during pregnancy, two of the identified randomized clinical trials addressed weight gain and also included biochemical validation of cessation (Chamberlain et al. 2017). One found a significant increase in weight gain by 8 months' gestation of 1.0 kilogram (kg) (2.2 pounds [lbs]) in the intervention versus the control group (Sexton and Hebel 1984); the other, which had fewer participants, found a 2.8-kg (6.2 lbs) unadjusted increase in weight gain among quitters compared with continuing smokers (Washio et al. 2011). This difference was no longer significant after adjustment for potential confounders (including pre-pregnancy BMI), but those possible confounders did not include gestational age at delivery. A significant increase in mean gestational weight gain per 10% increase in the number of negative smoking tests (during the course of the study) was not significant after adjustment for birth weight, suggesting that at least some of the potential effects of cessation on weight gain were from an increase in fetal growth (Washio et al. 2011).

Various observational studies have also found increased gestational weight gain in quitters compared with continuing smokers. Of six observational studies published since 2000, one examined gestational weight gain among women by smoking status across two consecutive pregnancies (Abrevaya 2008), and five examined this outcome by smoking status in individual pregnancies (Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Blatt et al. 2015; Hulman et al. 2016) (Table 4.31). Each of the latter five studies examined cessation at different time points in the conception and timing of pregnancy: two examined cessation before pregnancy (Favaretto et al. 2007; Blatt et al. 2015), four examined cessation during pregnancy (Favaretto et al. 2007; Adegboye et al. 2010; Blatt et al. 2015; Hulman et al. 2016), and two examined cessation by combining those who quit before and during pregnancy (Favaretto et al. 2007; Rode et al. 2013). None of the five studies compared gestational weight gain or rate of weight gain before and after smoking cessation. Four of the five studies (Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Hulman et al. 2016) adjusted for at least some potential confounders (including pre-pregnancy BMI) in some of the analyses. Four of the five studies (Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Hulman et al. 2016) assessed gestational weight gain using recommendations from the IOM, which are specific for pre-pregnancy BMI (Rasmussen et al. 2009).

In the single study examining weight gain by smoking status across pregnancies, Abrevaya and colleagues (2008) found a significantly greater gain in gestational weight during the second pregnancy among women who quit smoking between pregnancies compared with those who smoked during both pregnancies, even after adjusting for potential confounders. However, a limitation of this study was that smoking patterns were reduced to a few simplified categories. If smoking cessation during pregnancy does increase weight gain, then the effect could have been missed using this approach.

All five of the studies of individual pregnancies found that gestational weight gain in quitters was higher than gestational weight gain in continuing smokers (range: 0.5–2.8 kg). The comparisons were statistically significant in three of the five studies (Adegboye et al. 2010; Rode et al. 2013; Blatt et al. 2015), and statistical comparisons were not presented in the other two studies (Favaretto et al. 2007; Hulman et al. 2016). Adegboye and colleagues (2010) found that women who quit smoking during the first trimester gained 1.5-kg more weight than women who continued to smoke during pregnancy (unadjusted, $p < 0.001$). Rode and colleagues (who combined women who quit smoking before and during pregnancy) reported weight gains of 15.9 kg in quitters and 13.3 kg in continuing smokers, and the differences were significant after adjustment. Blatt and colleagues found, in unadjusted analyses, that women who quit smoking in the first or second trimester gained 6.2- and 3.3-pounds (2.8 kg and 1.5 kg, respectively) more weight than women who continued to smoke during pregnancy (Blatt et al. 2015). Hulman and colleagues (2016) examined cessation during pregnancy and trajectories of gestational weight gain based on weight gain in the first trimester and rate of weight gain in the second and third trimesters. The authors reported higher projected weight gains of 2.7 kg (adjusted for pre-pregnancy BMI) in quitters compared with continuing smokers, but did not report whether the findings were statistically significant. Favaretto and colleagues (2007) found a modest increase in gestational weight gain in women who quit smoking before or during pregnancy compared with those who continued to smoke during pregnancy: unadjusted estimates extrapolated to delivery were 13.4 kg and 12.9 kg, respectively. However, the authors did not stratify results by the timing of cessation with conception and did not report results of significance testing for this portion of the analysis.

Four of the five studies examining individual pregnancies and comparing quitters with nonsmokers

Table 4.31 Studies on smoking cessation and gestational weight gain

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Sexton and Hebel (1984)	• Randomized controlled trial of a behavioral intervention to increase smoking cessation • Enrolled pregnant women <18 weeks' gestation who smoked at least 10 cigarettes/day at or just before pregnancy • n = 935 • Years of data collection not reported • Maryland	• Quit smoking by late pregnancy (8th month) • Continued smoking in late pregnancy (8th month) • Cessation confirmed with salivary thiocyanate collected during 8th month of pregnancy	Gestational weight gain during the 8th month of pregnancy	**Mean gestational weight gain**: • Control group: 11.9 kg • Intervention group: 12.9 kg • Difference: 1.0 kg • p <0.05	Results not adjusted for confounders or gestational age at last measurement Did not account for alcohol or substance use

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Favaretto et al. (2007)	• Prospective cohort study • n = 4,000 • 1991–1995 • Brazil	• Nonsmoker: Never smoked • Continued smoking: Smoking at least 1 cigarette/day as of study interview • Quit smoking: – >6 months before pregnancy – Between 6 months before pregnancy and conception – Between conception and mid-pregnancy • Smoking history ascertained from maternal interviews conducted during the second trimester	Gestational weight gain calculated using information from chart review; used last measured weight and extrapolated to delivery	**Mean gestational weight gain (SD):** • Measured: – Never smoked: 11.2 kg (5.8 kg) – Quit smoking (groups combined): 12.1 kg (6.1 kg) – Continued smoking: 11.7 (6.5 kg) • Extrapolated: – Never smoker: 12.4 kg (6.1 kg) – Quit smoking (groups combined): 13.4 kg (6.2 kg) – Continued smoking: 12.9 kg (6.8 kg) **Difference in gestational weight gain by timing of cessation (95% CI):** • Never smoked: Reference • Before conception: – Unadjusted: 0.14 kg (-0.54–0.81 kg) – Adjusted: 0.53 kg (-0.12–1.19 kg) • Quit <6 months before conception: – Unadjusted: 0.90 (0.19–1.62 kg) – Adjusted: 1.00 (0.32–1.69 kg) • Quit after conception through mid-pregnancy: – Unadjusted: 1.78 (0.98–2.57 kg) – Adjusted: 1.54 (0.78–2.31 kg) **Adjusted RR for weight gain in excess of IOM standards (95% CI):** • Never smoked: Reference • Quit overall: 1.2 (1.05–1.37) • Quit <6 months before conception: 1.14 (0.94–1.38) • Quit after conception through mid-pregnancy: 1.34 (1.10–1.63)	Results adjusted for maternal age, education, race, parity, clinical center, and pre-pregnancy BMI Did not account for alcohol or substance use

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Abrevaya et al. (2008)	• Population-based, retrospective cohort study • Linked Michigan certificates of live birth • First and second pregnancies in which women smoked during the first pregnancy • n = 14,731 (18–24 years of age) • n = 8,044 (25–30 years of age) • 1989–2004 • Michigan	• Smoking status across pregnancies • Quit smoking: Smoked during the first pregnancy, not during the second pregnancy • Continued smoking in both pregnancies • Smoking status based on smoking history collected for certificates of live birth, which used one question on tobacco use during pregnancy (yes/no)	Gestational weight gain obtained from certificates of live birth	**Difference in mean gestational weight gain among women who smoked during the first pregnancy (95% CI):** • Quit smoking: Reference • Continued smoking: – 18–24 years of age: -1.99 lbs (-2.50– -1.49 lbs) – 25–30 years of age: -2.10 lbs (-2.67– -1.54 lbs)	Results adjusted for maternal race, education, income, population, interpregnancy interval, year of birth, trimester of first prenatal visit, presence of father's name on birth certificate, number of prenatal visits, and first-birth value of the outcome Did not account for alcohol or substance use
Adegboye et al. (2010)	• Retrospective cohort study • Risk factors for postpartum weight retention • Singleton pregnancies • n = 1,753 • 1984–1985 • Sweden	• Nonsmokers: Did not smoke during pregnancy • Quit smoking: Quit smoking during first trimester and remained abstinent throughout pregnancy • Continued smoking: Continued to smoke during pregnancy • Smoking status based on self-reports but details not reported	Gestational weight gain calculated by subtracting maternal weight at the end of gestation from self-reported pre-pregnancy weight Compared with IOM (2009) recommendations	**Unadjusted mean gestational weight gain (SD):** • Nonsmoker: 14.1 kg (4.0 kg) • Quit smoking: 15.3 kg (4.4 kg) • Continued smoking: 13.8 kg (4.3 kg) • p <0.001, ANOVA **OR (95% CI) for gestational weight gain in excess of IOM recommendations:** • Nonsmoker: Reference • Quit smoking: – Unadjusted: 1.6 (1.1–2.1) – Adjusted: 2.0 (1.4–3.0) • Continued smoking: – Unadjusted: 1.0 (0.8–1.3) – Adjusted: 1.3 (0.9–1.8)	Results adjusted for birth weight, gestational age, parity, pre-pregnancy BMI, alcohol consumption, physical activity, and breakfast frequency Did not account for substance use

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Washio et al. (2011)	• Randomized controlled trial of a voucher incentive to increase smoking cessation • Pregnant smokers • n = 154 • 2001–2006 • Vermont	• Quit smoking: Past 7-day abstinence confirmed by urine cotinine at the end of pregnancy • Continued smoking: Not abstinent at the end of pregnancy • Not reported when cessation data were collected	Weight at delivery and pre-pregnancy weight	**Mean gestational weight gain (SD):** • Control group: 15.0 +/- 0.8 kg – Intervention group: 15.0 +/- 0.9 kg – Difference = 0.0 kg – p = 0.97 • Quit smoking: 17.2 +/- 1.1 kg – Continued smoking: 15.4 +/- 0.6 kg – Difference = 2.8 kg – p = 0.04 **Adjusted mean difference in gestational weight gain:** • Quit smoking vs. continued smoking: – 2.4 kg – p = 0.06 • Mean increase in gestational weight gain of 0.34 kg per 10% increase in cessation: – p = 0.03 (results adjusted for pre-pregnancy BMI and parity) – p = 0.13 (results adjusted for pre-pregnancy BMI, parity, and birth weight)	Loss of significance after adjustment for birth weight suggests that the increase in gestational weight gain in quitters compared with continuing smokers was attributable in part to increased fetal growth

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Rode et al. (2013)	• Prospective cohort of pregnant women who received an intervention to be smokefree • Singleton, term pregnancies • n = 1,774 • 1996–1999 • Denmark	• Nonsmokers: Not defined • Quit smoking: Quit immediately before or during pregnancy • Continued smoking: Not further defined • Smoking status based on self-reports assessed at 12–18 weeks' and 37 weeks' gestation and 1 year postpartum • Salivary cotinine obtained in a subgroup at 16 and 37 weeks' gestation	Gestational weight gain at 37 weeks' gestation compared with recommendations from IOM (2009)	**Mean gestational weight gain at 37 weeks (SD), difference in gestational weight gain (95% CI):** • Nonsmokers: 13.46 kg (4.71 kg) (reference) • Quit smoking: – Unadjusted: 2.44 kg (1.86–3.03 kg) – Adjusted: 2.01 kg (1.51–2.64 kg) **Adjusted OR (95% CI) for gestational weight gain in excess of IOM recommendations:** • Nonsmokers: Reference • Quit smoking: 1.9 (1.5–2.4) • Continued smoking: 1.2 (0.9–1.5)	Weight gain adjusted for pre-pregnancy BMI, gestational age, and parity Salivary cotinine for subgroup reported but report did not describe whether it was integrated into main analysis Did not account for alcohol or substance use OR for gaining in excess of IOM recommendations adjusted for gestational age and preeclampsia
Blatt et al. (2015)	• Population-based retrospective cohort study • Ohio certificates of live birth • n = 927,424 • 2006–2012 • Ohio	• Nonsmoker: Did not smoke during the 3 months before pregnancy or during pregnancy • Quit smoking before pregnancy: Smoked during the 3 months before pregnancy but not during pregnancy • Quit smoking first trimester: Smoked first trimester only • Quit smoking second trimester: Smoked first and second trimester, not third • Continued smoking: Smoked throughout pregnancy • Smoking history ascertained from vital statistics data and certificates of live birth	Gestational weight gain calculated from maternal weight at delivery vs. preconception weight	**Mean gestational weight gain (SD):** • Nonsmoker: 31.2 lbs (+/- 16.9 lbs) • Quit smoking before pregnancy: 36.4 lbs (+/- 18.8 lbs) • Quit smoking first trimester: 36.5 lbs (+/- 19.2 lbs) • Quit smoking second trimester: 33.6 lbs (+/- 19.5 lbs) • Continued smoking: 30.3 lbs (+/- 8.9 lbs) • All comparisons: p <0.001	Findings not adjusted for potential confounders Did not account for alcohol or substance use

Table 4.31 Continued

Study	Study design	Tobacco exposure	Outcome definition	Results	Comments
Hulman et al. (2016)	• Longitudinal cohort study • Singleton pregnancies • n = 509 • 2013 • Ontario, Canada	• Nonsmokers: Women who never smoked • Quit smoking: Smoked previously but quit when they found out they were pregnant • Continued smoking: Still smoking at study assessment • Smoking status based on maternal self-reports obtained during survey conducted at ~32 weeks' gestation	Gestational weight gain calculated from pre-pregnancy weight (or first available antenatal visit) and serial weight measurements obtained from medical record review Rate of weight gain (kg/week) in second and third trimesters compared with recommendations from IOM: • Underweight: 0.44–0.58 • Normal: 0.35–0.50 • Overweight: 0.23–0.33 • Obese: 0.17–0.27	**Mean gestational weight gain (95% CI) based on trajectories for the end of the 39th week:** • Nonsmoker: 14 kg • Quit smoking: 16.7 kg (15.1–18.4 kg) • Continued smoking: 14 kg **Total first trimester gestational weight gain (95% CI):** • Nonsmoker: 1.7 kg (1.4–2.1 kg) • Quit smoking: 1.2 kg (0.3–2.1 kg) • Continued smoking: 3.5 kg (2.4–4.6 kg) **Rate of weight gain in second and third trimesters:** • Quit smoking: 0.60 kg/week (0.54–0.65 kg/week) • Vs. nonsmokers: +22% (11–34%) • Vs. continued smokers: +53% (32–75%) **Rate of weight gain by IOM categories: kg/week (95% CI):** • Nonsmoker: – Underweight: 0.52 (0.42–0.62) – Normal: 0.51 (0.49–0.54) – Overweight: 0.52 (0.48–0.55) – Obese: 0.38 (0.33–0.42) • Quit smoking: – Underweight: 0.62 (0.50–0.73) – Normal: 0.61 (0.56–0.67) – Overweight: 0.62 (0.56–0.68) – Obese: 0.48 (0.41–0.54) • Continued smoking: – Underweight: 0.44 (0.33–0.56) – Normal: 0.44 (0.37–0.50) – Overweight: 0.44 (0.37–0.51) – Obese: 0.30 (0.23–0.37)	Results adjusted for maternal age, race, parity, marital status, education, income, and BMI Did not account for alcohol or substance use

Notes: **ANOVA =** analysis of variance; **BMI =** body mass index; **CI =** confidence interval; **IOM =** Institute of Medicine; **kg =** kilograms; **lbs =** pounds; **OR =** odds ratio; **RR =** relative risk; **SD =** standard deviation.

(Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Blatt et al. 2015) found a significant increase in gestational weight gain in quitters (range: 0.5–2.4 kg). One study did not report statistical comparisons (Hulman et al. 2015). The two studies examining cessation before pregnancy both found significant increases in gestational weight gain among women who quit before but close to the time of conception in comparisons with nonsmokers (range: 1.0–2.4 kg) (Favaretto et al. 2007; Blatt et al. 2015). The study by Favaretto and colleagues (2007) also found that weight gain in women who had quit more than 6 months before conception did not differ significantly from that of nonsmokers, even after adjusting for potential confounders. Of the four studies examining cessation during pregnancy, three (Favaretto et al. 2007; Adegboye et al. 2010; Blatt et al. 2015) reported significant increases in weight in quitters compared with nonsmokers. Adegboye and colleagues (2010) and Blatt and colleagues (2015) examined cessation in the first trimester, which was associated with increases in weight gain of 1.2 kg (Adegboye et al. 2010) and 1.1 kg (Blatt et al. 2015), respectively. Blatt and colleagues (2015) also described a significant increase in weight gain (2.4 kg) among women who quit during the second trimester in a comparison with nonsmokers. Favaretto and colleagues (2007) examined cessation between conception and mid-pregnancy (20–28 weeks gestation) and found a 1.54-kg increase in weight gain in quitters compared with nonsmokers after adjusting for pre-pregnancy BMI and other potential confounders. Hulman and colleagues (2016) also examined cessation during pregnancy and reported that projected gestational weight gain, based on weight gain trajectories and adjusted for confounders, was higher by 2.7 kg in quitters than in nonsmokers, but results of testing for statistical significance were not presented. Rode and colleagues reported a 2.0-kg (95% CI, 1.5–2.6 kg) increase in adjusted gestational weight gain in women who quit smoking before or during pregnancy compared with women who were nonsmokers (Rode et al. 2013).

Two of the four studies examining cessation during pregnancy also compared weight gain early and late in pregnancy. Rode and colleagues (2013) found that at 16 weeks' gestation no differences existed in weight gain when nonsmokers, women who quit before or during pregnancy, and continuing smokers were compared after adjustment for pre-pregnancy BMI, gestational age, and parity. By 37 weeks' gestation, however, women who had quit smoking had a significant, adjusted 4.4-lb [2.0 kg] increase in weight gain in comparison with nonsmokers, while continuing smokers and nonsmokers did not experience relative increases in weight gain. In contrast, Hulman and colleagues (2016) found that continuing smokers gained more than twice as much weight during the first trimester as women who quit smoking upon learning of their pregnancy (adjusted difference = 3.0 kg [6.6 lbs] after controlling for sociodemographic characteristics and pre-pregnancy BMI). The weekly rate of weight gain in the second and third trimesters was highest, however, in women who quit smoking during pregnancy. Quitters had a 22% faster rate of weight gain in the second and third trimesters of pregnancy compared with nonsmokers and a 53% faster rate of weight gain compared with continuing smokers (Hulman et al. 2016).

Four studies (Favaretto et al. 2007; Adegboye et al. 2010; Rode et al. 2013; Hulman et al. 2016) examined gestational weight gain with respect to IOM recommendations (IOM 1990). Two studies (Favaretto et al. 2007; Adegoye et al. 2010) found that women who quit smoking during pregnancy were significantly more likely to gain weight in excess of IOM recommendations compared with nonsmokers, even after controlling for pre-pregnancy BMI and other factors (adjusted RR: 1.34 [95% CI, 1.10–1.63]; and adjusted OR: 2.0 [95% CI, 1.4–3.0], respectively). Rode and colleagues (2013) found that the percentage of women who gained in excess of IOM guidelines differed significantly by smoking status (45.9%, 34.6%, and 31.3% for women who quit before or during pregnancy, continuing smokers, and nonsmokers, respectively, $P < 0.001$), and after adjustment for gestational age and preeclampsia, quitters were significantly more likely to gain in excess of IOM recommendations than nonsmokers (OR 1.9 95% CI 1.5-2.4). Adjusted models comparing quitters with continuing smokers were not reported (Rode et al. 2013). Hulman and colleagues (2016) examined IOM recommendations for rate of weight gain and found that women who quit smoking during pregnancy on average gained above the rate recommended by the IOM in the second and third trimesters for all pre-pregnancy BMI categories, and weight gain by women who continued to smoke varied by pre-pregnancy BMI category (under- and normal-weight women on average gained within the recommended rate range while overweight and obese women gained faster than the recommended rate). Among nonsmokers, only those who were underweight gained at a rate within IOM recommendations; all other groups gained at a rate exceeding IOM recommendations (Hulman et al. 2016).

Summary of the Evidence

The evidence describing the associations between smoking status, quitting, and gestational weight gain has expanded considerably since the 1990 Surgeon General's report, but there has been some variation in the covariates included in the analytic models and in the time points used to define smoking cessation (e.g., preconception, in early gestation, by mid-pregnancy, during gestation).

Nonetheless, the evidence is sufficient to infer that women who quit smoking shortly before or during pregnancy gain more weight during gestation than women who continue to smoke, and the findings are consistent, including data from two randomized clinical trials. The evidence is suggestive but not sufficient to infer that women who quit smoking before or during pregnancy gain more weight during gestation than nonsmokers. The evidence is suggestive but not sufficient to infer that women who quit smoking before or during pregnancy are at increased risk of excess weight gain, per IOM guidelines, compared with nonsmokers. However, very little evidence could be used to compare the risk of excess gestational weight gain in quitters with that in continuing smokers.

Prenatal smoking cessation has substantial health benefits for mothers and offspring, and providing assistance with weight management while promoting smoking cessation could help to optimize outcomes.

Gestational Diabetes

Gestational diabetes mellitus (GDM), which is defined as carbohydrate intolerance leading to hyperglycemia with onset or first recognition during pregnancy, affects 4% to 9% of pregnancies in the United States (DeSisto et al. 2014). Although this complication usually resolves after delivery, up to one-third of affected women have diabetes or impaired glucose metabolism at postpartum screening. Women with GDM are at increased risk for cesarean delivery, and their infants are at increased risk for macrosomia (i.e., being large for gestational age), neonatal hypoglycemia, and fetal hyperinsulinemia (Hyperglycemia and Adverse Pregnancy Outcome Study Cooperative Research Group 2008). Most women who develop GDM have preexisting impaired beta cell function and chronic insulin resistance that is characteristic of type 2 diabetes, and women with a history of GDM are at substantially increased risk for the future development of type 2 diabetes, providing evidence of a common underlying mechanism (Mack and Tomich 2017). Furthermore, GDM is consistently associated with both higher prepregnancy BMI and excessive gestational weight gain (Brunner et al. 2015; Najafi et al. 2019).

The 1990 Surgeon General's report did not examine smoking and GDM, but the 2001 Surgeon General's report on women and smoking described inconsistent evidence of an association between smoking and GDM (USDHHS 2001). The 2014 Surgeon General's report did not examine smoking and GDM, but did conclude that smoking is causally associated with type 2 diabetes and did address smoking cessation and risk of type 2 diabetes (USDHHS 2014). In one large study, the risk of incident type 2 diabetes for short-term quitters was higher than that of current smokers but decreased to the level for never smokers by 12 years (Yeh et al. 2010; USDHHS 2014). In another large study, the risk of type 2 diabetes decreased to that of nonsmokers 5 years after quitting in women and 10 years after quitting in men (Will et al. 2001; Wendland et al. 2008; USDHHS 2014). The transient increase in risk for quitters may be the result of short-term effects on weight gain. The 2014 report did not address GDM specifically.

In light of the potential for increased short-term morbidity associated with weight gain following smoking cessation, an increase in gestational weight gain associated with smoking cessation could be associated with adverse pregnancy outcomes, such as GDM or macrosomia, regardless of whether smoking itself is directly causally associated with GDM (Rasmussen et al. 2009). Therefore, smoking cessation and GDM were reviewed in this section absent an established causal relationship between active smoking and GDM in these reports.

Five studies on smoking and GDM published since the 2001 report included prevalence estimates for GDM among nonsmokers, former smokers, and continuing smokers (England et al. 2004; Fasting et al. 2009; Erickson and Arbour 2012; Räisänen et al. 2014; Blatt et al. 2015). Three of these were large, population-based studies (Erickson and Arbour 2012; Räisänen et al. 2014; Blatt et al. 2015), and two were small, clinic-based studies (England et al. 2004; Fasting et al. 2009). Räisänen and colleagues (2014) reported a greater prevalence of GDM among women who quit smoking in the third trimester (9.8%) compared with never smokers (7.6%) and with continuing smokers (7.6%); Erickson and Arbour (2012) reported the lowest GDM prevalence in continuing smokers (3.8% to 4.9%), with prevalence equaling 5.4% in quitters and 6.7% in nonsmokers; and Blatt and colleagues (2015) reported the lowest prevalence in nonsmokers (5.4%) and a slightly higher prevalence in preconception quitters (5.8%) and in first- and second-trimester quitters (5.6% and 5.5%, respectively). In none of these three studies was GDM the primary outcome of interest, and none reported results of testing for statistical significance in direct comparisons or the results of adjusted analyses. The study populations in these analyses were very large, however.

In one of the two smaller studies, England and colleagues (2004) reported a significant increase in mean adjusted plasma glucose concentration after a 1-hour, 50-g glucose challenge in continuing smokers compared with never smokers (112.6 milligrams per deciliter [mg/dL] vs. 108.3 mg/dL, $p < 0.01$), but no differences were seen when never smokers were compared with women who had quit before pregnancy (108.5 mg/dL) or during pregnancy (109.5 mg/dL). Compared with nonsmokers, continued smoking was significantly associated with GDM (aOR = 1.9; 95% CI, 1.0–3.6), but no significant associations were

observed for smoking with cessation before (aOR = 0.8; 95% CI, 0.3–2.1) or during pregnancy (aOR = 1.4; 95% CI, 0.5–2.9) (England et al. 2004). In the other of the smaller studies, Fasting and colleagues (2009) reported identical estimates of GDM prevalence (3%) for never smokers and smokers who quit early in pregnancy and an estimate of 5% for women who continued to smoke. GDM was not the primary outcome of interest, however, and the number of GDM cases was small (only three each in the groups of quitters and continuing smokers), and an adjusted analysis was not performed.

Summary of the Evidence

Only a limited number of studies on the relationship between smoking cessation and GDM were identified, and in the majority of those studies, GDM was not the main outcome of interest, potentially limiting assessment for relevant covariates and confounders. Thus, the evidence is inadequate to determine whether smoking cessation during pregnancy increases the risk of gestational diabetes.

Birth Outcomes

Birth Defects

The 2014 Surgeon General's report concluded that there was sufficient evidence to infer a causal relationship between maternal smoking in early pregnancy and increased risk for orofacial clefts (USDHHS 2014). However, the evidence was suggestive but not sufficient to infer an increased risk for other birth defects—including clubfoot, gastroschisis, and atrial septal heart defects—for women who smoke in early pregnancy (USDHHS 2014). Based on the available scientific evidence, the 2014 report recommended providing information on the risk of orofacial clefts as part of efforts to reduce smoking prior to conception and in early pregnancy (USDHHS 2014); however, few studies have specifically assessed the risk for orofacial clefts among women who are former smokers. One study has assessed the risk for any major anomaly among women who quit smoking during the first trimester compared with women who did not smoke during pregnancy (Räisänen et al. 2014). However, due to the limited number of studies published to date specifically related to cessation and risk for specific birth defect categories, including orofacial clefts, this report does not reach any new conclusions regarding these outcomes.

Fetal Growth and Birth Weight

The effects of maternal smoking on birth weight have been recognized since the 1964 Surgeon General's report, which found that infants of smokers were more likely than those of nonsmokers to weigh less than 2,500 g at birth (USDHEW 1964). Birth weight is determined by both gestational age at delivery and the rate of fetal growth, and subsequent Surgeon General's reports have addressed these factors separately when examining birth weight as an outcome. The 1990 Surgeon General's report noted that the risk of being small for gestational age (typically defined as weight ≤10th percentile for gestational age) was 3.5- to 4-fold higher in infants of smokers than in infants of nonsmokers (USDHHS 1990). The report concluded that babies of women who quit smoking before conception did not experience smoking-related reductions in fetal growth, while cessation before the third trimester significantly attenuated the deleterious effects of maternal smoking on fetal growth (USDHHS 1990). The 2004 Surgeon General's report found sufficient evidence to infer a causal relationship between smoking and both fetal growth restriction and reduced gestational age/increased preterm delivery (USDHHS 2004). It confirmed the 1990 Surgeon General's report's finding that cessation eliminates much of the reduction in birth weight caused by maternal smoking (USDHHS 2004). The 2014 Surgeon General's report explored in depth the relationships between smoking and fetal growth. The report concluded that nicotine is unlikely to be the main contributor in tobacco smoke to fetal growth restriction, with products of combustion likely playing a major role in this regard (USDHHS 2014). This report did not address the benefits of smoking cessation, however.

Several subsequent studies have supported the conclusions of the 1990 and 2004 Surgeon General's reports that smoking cessation attenuates the adverse effects of smoking on fetal growth and birth weight. There are several methodologic challenges, however, in studies of fetal growth and birth weight. First, fetal growth is not linear, and the most rapid rate of growth occurs in the third trimester (Kiserud et al. 2017). As a consequence, assessing the timing of tobacco exposure with respect to position on the fetal growth curve is essential to characterizing the mechanisms through which tobacco use exerts adverse effects and cessation benefits fetal growth. Many of the studies identified in the literature review, however, did not assess tobacco use and cessation across the entire pregnancy. Second, as previously described, smokers typically differ from nonsmokers in numerous behavioral, obstetrical, and other health-related factors, and a failure to control for potential confounders may result in residual confounding. High-quality data on many potentially important exposures for fetal growth, such as use of alcohol and/or illicit drugs, are often lacking in registries and other commonly used sources of data.

Birth Weight

Table 4.32 presents 40 studies that examined birth weight and smoking cessation during pregnancy. Studies varied in the use of biochemical validation of reported cessation, in descriptions about the timing of cessation, and in adjustments for potential confounders. Twenty of the studies addressed gestational age by restricting the analysis to term infants and/or adjusting for gestational age (Hrubá and Kachlik 2000; Lindley et al. 2000; England et al. 2001a,b, 2007; Mendez et al. 2008; Nijiati et al. 2008; Sasaki et al. 2008; Andersen et al. 2009; Kabir et al. 2009; Prabhu et al. 2010; Vardavas et al. 2010; Bakker et al. 2011; Benjamin-Garner and Stotts 2013; Juarez and Merlo 2013; Miyake et al. 2013; Rode et al. 2013; Slatter et al. 2014; Suzuki et al. 2014, 2016; Hayes et al. 2016); 25 included adjustment for at least some additional confounders (Lindley et al. 2000; England et al. 2001a,b, 2007; Dejmek et al. 2002; Wen et al. 2005; Abrevaya 2008; Nijiati et al. 2008; Sasaki et al. 2008; Andersen et al. 2009; McCowan et al. 2009; Prabhu et al. 2010; Vardavas et al. 2010; Bakker et al. 2011; Benjamin-Garner and Stotts 2013; Himes et al. 2013; Juarez and Merlo 2013; Miyake et al. 2013; Murphy et al. 2013; Rode et al. 2013; Meghea et al. 2014; Suzuki et al. 2014, 2016; Bailey 2015; Yan and Groothuis 2015; Hayes et al. 2016); and 9 included biochemical validation of smoking cessation (England et al. 2001a,b; Secker-Walker and Vacek 2002; Malchodi et al. 2003; England et al. 2007; Andersen et al. 2009; Benjamin-Garner and Stotts 2013; Rode et al. 2013; Bailey 2015; Hayes et al. 2016). Five studies did not differentiate between either quitting before pregnancy and quitting during early pregnancy or a combination of both and, thus, could not isolate the effects of quitting during pregnancy (Hrubá and Kachlik 2000; England et al. 2007; Vardavas et al. 2010; Murphy et al. 2013; Rode et al. 2013). Nineteen studies used smoking status in late pregnancy to categorize exposure groups, thus those studies did not combine late quitters with continuing smokers, or women who relapsed with women who remained abstinent (Lindley et al. 2000; England et al. 2001a,b, 2007; Dejmek et al. 2002; Secker-Walker and Vacek 2002; Malchodi et al. 2003; Andersen et al. 2009; Bakker et al. 2011; Benjamin-Garner and Stotts 2013; Himes et al. 2013; Juarez and Merlo 2013; Miyake et al. 2013; Murphy et al. 2013; Rode et al. 2013; Slatter et al. 2014; Bailey 2015; Blatt et al. 2015; Yan and Groothuis 2015; Wallace et al. 2017). Only two studies adjusted for or otherwise addressed alcohol and other substance use (Murphy et al. 2013; Bailey 2015), and seven adjusted for alcohol use but not other substance use (Dejmek et al. 2002; Wen et al. 2005; Sasaki et al. 2008; McCowan et al. 2009; Bakker et al. 2011; Miyake et al. 2013; Yan and Groothuis 2015), and one excluded women who used illicit drugs (Himes et al. 2013). Five studies accounted for gestational age and also adjusted for confounders, included biochemical validation of quit status, and incorporated well-defined exposure groups that included smoking status in late pregnancy (England et al. 2001a,b, 2007; Andersen et al. 2009; Benjamin-Garner and Stotts 2013; Rode et al. 2013). None of these five adjusted for alcohol or illicit drug use.

Despite these methodologic differences, most of the 40 studies found that (a) women who continued to smoke past early pregnancy delivered infants of lower birth weight than those of nonsmokers and (b) cessation before or during pregnancy attenuated or eliminated this effect. These findings were consistent in studies controlling for gestational age at birth and/or excluding preterm deliveries (Lindley et al. 2000; England et al. 2001b, 2007; Mendez et al. 2008; Nijiati et al. 2008; Sasaki et al. 2008; Andersen et al. 2009; Kabir et al. 2009; Prabhu et al. 2010; Vardavas et al. 2010; Bakker et al. 2011; Juarez and Merlo 2013; Miyake et al. 2013; Rode et al. 2013; Slatter et al. 2014; Suzuki et al. 2014, 2016) and in studies that addressed illicit drug and/or alcohol use (Dejmek et al. 2002; Wen et al. 2005; Sasaki et al. 2008; McCowan et al. 2009; Bakker et al. 2011; Himes et al. 2013; Miyake et al. 2013; Murphy et al. 2013; Bailey 2015; Yan and Groothuis 2015).

Four of the 40 studies validated smoking status while also adjusting for gestational age or restricting the study to term births, adjusting for potential confounders, and assessing smoking status in late pregnancy. Results from the two studies comparing quitters with nonsmokers found no difference in mean adjusted birth weight (England et al. 2007; Andersen et al. 2009), and the other two studies were randomized clinical trials of cessation interventions and thus compared quitters with continuing smokers (England et al. 2001b; Benjamin-Garner and Stotts 2013). In these two studies, the adjusted mean difference in birth weight between infants of quitters and those of continuing smokers was an excess of 100 and 300 g, respectively. However, England and colleagues (2007) combined women who quit before pregnancy with women who quit during pregnancy and, thus, could not address the effect of cessation during pregnancy.

One large study (previously described) used a sibling-comparison analysis to address the problem of potential uncontrolled confounding in the relationship between smoking during pregnancy and the birth weight of offspring (Juarez and Merlo 2013). Compared with the conventional analysis performed with all singleton births in the dataset, the sibling analysis revealed a reduced effect of smoking on gestational age–adjusted birth weight. In the sibling analysis, continuous smoking through pregnancy reduced birth weight by 162 g for light smokers (≤10 cigarettes per day) and by 226 g for heavy smokers (>10 cigarettes per day), versus reductions of

Table 4.32 Studies on smoking cessation and birth weight

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Hrubá and Kachlik (2000)	• Retrospective, clinic-based study • Term, singleton deliveries • n = 1,147 • Years of data collection not reported • Czech Republic	• Nonsmokers: Never smoked • Quit smoking: Smoked but quit before pregnancy or during the first trimester • Continued smoking: Smoked throughout pregnancy, either daily or occasionally • Smoking status based on self-report from interview conducted shortly after delivery	**Mean birth weight (SD) and difference in mean birth weight (among women without exposure to secondhand smoke):** • Nonsmokers: 3,383 g (456) (reference) • Quit smoking: 3,414 g (459), +31 g • Continued smoking: 3,298 g (484), -85 g	Analysis restricted to term births Results not adjusted for potential confounders Analysis stratified by exposure to secondhand smoke Did not account for alcohol or illicit drug use
Lindley et al. (2000)	• Population-based, retrospective cohort study • Analysis of births from the Swedish Birth Registry • ≥32 weeks' gestation at delivery, excluded pregnancies with complication or congenital malformations • n = 15,185 • 1991–1992 • Sweden	• Nonsmoker: Not a smoker or less than daily smoker at first prenatal visit • Quit smoking: Smoked daily at first prenatal visit but did not smoke at late visit • Continued smoking: Smoked at first and late prenatal visits: – Light smoker: 1–9 cigarettes/day – Heavy smoker: ≥10 cigarettes/day • Smoking status based on self-reports at first and late (~32 weeks) prenatal visits	**Mean adjusted birth weight and difference in mean adjusted birth weight:** • Nonsmokers: 3,459 g, p <0.001 • Quit smoking: -26 g (not significant) • Continued smoking – Light smokers: -136 g, p <0.001 – Heavy smokers: -175 g, p <0.001	Results adjusted for sex of the infant, gestational age, parity, maternal age, height, and BMI Did not account for alcohol or illicit drug use
England et al. (2001b)	• Randomized clinical trial of a smoking cessation intervention • Singleton, term pregnancies • n = 926 • 1987–1991 • Multiple centers in the United States	• Quit smoking before enrollment: Smoked within 1 week of learning they were pregnant but quit by enrollment • Quit smoking after enrollment: Smoked within 1 week of learning they were pregnant and at enrollment but quit after enrollment • Continued to smoke: – Did not change: Cotinine, cigarettes/day changed by <50% – Reduced: Reduced cotinine, cigarettes/day by >50% – Increased: Increased cotinine, cigarettes/day by >50% • Smoking status based on self-report obtained at enrollment and in the third trimester, validated using urine cotinine collected concurrently	**Mean adjusted birth weight (95% CI) and difference in mean adjusted birth weight (95% CI)** • Self-report: – Continued to smoke/did not change: 3,205 g (reference) – Quit smoking after enrollment: • +286 g (196–376 g) • Cotinine validated: – Continued to smoke/did not change: 3,216 g (reference) – Quit smoking after enrollment: • +197 g (94–301 g) • Mean adjusted birth weight of those who reduced or increased cotinine or cigarettes/day did not differ from that of women who did not change	Only smokers enrolled; no nonsmoker comparison group Analysis restricted to term births Results adjusted for maternal age, parity, race, BMI, state of clinic's location, sex of the infant, and gestational age Did not account for alcohol or illicit drug use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
MacArthur et al. (2001)	• Randomized clinical trial of a behavioral intervention of antismoking education with long-term follow-up • n = 1,853 • 1981–1982 • Alabama	• Nonsmokers: Not smoking at enrollment • Quit smoking by 6 weeks • Quit smoking 7–16 weeks • Quit smoking ≥17 weeks • Continued smoking • Smoking status based on self-reports at enrollment into prenatal care	**Unadjusted mean birth weight and difference in mean birth weight:** • Nonsmokers: 3,455 g (reference) • Quit by 6 weeks: 3,433 g, -12 g • Quit 7-16 weeks: 3,389 g, -56 g • Quit ≥17 weeks: 3,327 g, -118 g • Continued smoking: 3,149 g, -296 g	Results not adjusted for potential confounders Did not account for alcohol or substance use Direct statistical comparisons between groups not shown
Dejmek et al. (2002)	• Population-based retrospective cohort • n = 6,866 • 1994–1999 • Czech Republic	• Nonsmoker: Not smoking when pregnancy recognized • Quit after pregnancy recognized: • Moderate smokers: 1–10 cigarettes/day • Heavy smokers: >10 cigarettes/day • Continued smoking: • Moderate smokers: 1–10 cigarettes/day • Heavy smokers: >10 cigarettes/day • Smoking status based on self-reports obtained at delivery	**Difference in mean adjusted birth weight (95% CI):** • Nonsmoker (reference) • Quit after pregnancy recognized: – Moderate smoker: -22 g (-64–19 g) – Heavy smoker: -66 g (-146–14 g) • Continued smoking: – 1–10 cigarettes/day: -152 g – (-185– -117 g) – >10 cigarettes/day: -259 g – (-342– -175 g)	Results adjusted for maternal age, district, ethnicity, education, parity, sex, height, pre-pregnancy weight, alcohol consumption, and season Did not account for illicit drug use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Secker-Walker and Vacek (2002)	• Randomized clinical trial of a smoking cessation intervention • Singleton births • n = 240 • 1988–1992 • Vermont	• Quit smoking: Smoked at enrollment but quit in late pregnancy (~35 weeks' gestation) • Continued smoking: Smoked at enrollment and in late pregnancy: – Reduced by <50% – Reduced by ≥50% • Smoking status based on self-reports and urine cotinine obtained at enrollment into prenatal care [14.6 (7.0) weeks] and near the end of pregnancy [35.0 (1.2) weeks]	**Mean infant birth weight (95% CI):** • Self-report (adjusted results were adjusted for number of cigarettes smoked/day at first visit): – Reduced <50%: ○ Unadjusted: 3,203 g (3,127–3,278 g) ○ Adjusted: 3,203 g (3,128–3,278 g) – Reduced ≥50%: ○ Unadjusted: 3,239 g (3,096–3,382 g) ○ Adjusted: 3,267 g (3,124–3,410 g) – Quit: ○ Unadjusted: 3,446 (3,298–3,594 g) ○ Adjusted: 3,413 g (3,270–3,556 g) • With biochemical validation (adjusted results were adjusted for cotinine concentration at first visit): – Reduced <50%: ○ Unadjusted: 3,205 g (3,124–3,286 g) ○ Adjusted: 3,214 g (3,133–3,295 g) – Reduced ≥50%: ○ Unadjusted: 3,184 g (3,069–3,298 g) ○ Adjusted: Reduced 3,226 g (3,114–3,338 g) – Quit (based on self-reports): ○ Unadjusted: 3,465 g (3,306–3,624 g) ○ Adjusted: 3,447 g (3,291–3,604 g) **Difference in mean adjusted infant birth weight:** • Quit vs. reduced <50%: – Self-report: 210 g – Cotinine validated: 233 g	All study participants were smokers at the time of recruitment; no nonsmoker comparison group Did not account for alcohol or illicit drug use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Malchodi et al. (2003)	• Randomized clinical trial of a smoking cessation intervention • n = 142 • 1998–2000 • Connecticut	• Quit smoking: Smoked daily in the week before learning they were pregnant but quit by 36 weeks' gestation • Continued smoking: Smoked daily in the week before learning they were pregnant and were still smoking at 36 weeks' gestation: – 1–6 cigarettes/day – >6 cigarettes/day • Smoking status based on self-reports • Quit status confirmed with both expired CO and urine cotinine collected at 36 weeks	**Mean birth weight (SD):** • Continued smoking, 1–6 cigarettes/day: 3,071 g (525) • Continued smoking, >6 cigarettes/day: 2,841 g (447) • Quit smoking: 3,289 g (592) **Difference in mean birth weight:** • Quit smoking vs. continued smoking >6 cigarettes/day: +448 g, p <0.01	All study participants were smokers; no nonsmoker comparison group Results not adjusted for potential confounders Authors reported that no baseline variables were associated with infant birth weight Did not account for alcohol or illicit drug use
Vogazianos et al. (2005)	• Population-based retrospective cohort • n = 59,014 • 1990–1996 • Cyprus	• Nonsmoker: Did not smoke before or during pregnancy • Quite smoking: Smoked before but not during pregnancy; not clear how many women quit smoking during pregnancy and how they were categorized • Continued smoking: Smoked before and during pregnancy • Smoking status based on retrospective self-reports; exact timing of data collection not reported	**Mean birth weight:** • Nonsmoker: 3,254 g • Quit smoking: 3,258 g • Continued smoking: 3,162 g **Difference in mean birth weight (95% CI):** • Quit smoking vs. nonsmoker: +4 g (-29–37 g) • Continued smoking vs. nonsmoker: -92 g (-124– -59 g)	Results not adjusted for potential confounders Did not account for alcohol or illicit drug use
Wen et al. (2005)	• Wen et al. (2005) • Pregnancy Risk Assessment Monitoring System • Singleton, live births • n = 9,499 • 1989–1992 • Taipei City, Taiwan	• Nonsmokers: Details not provided • Quit smoking: Quit by the time of the first prenatal visit in the first trimester; not clear if this included those who quit before pregnancy • Continued smoking: Smoked after the first visit in the first trimester • Smoking status based on self-reports	**Mean adjusted birth weight (SD) and difference in mean adjusted birth weight:** • Continuing smokers: 3,027 g (450) (reference) • Nonsmokers: 3,184 g (430 g), +157 g, p <0.05 • Quit smoking: 3,195 g (447 g), +168 g, p <0.05	Results not adjusted for maternal age, parity, alcohol use, and sex of the infant Did not account for illicit drug use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
England et al. (2007)	• Randomized trial for preeclampsia prevention • Nulliparous women • n = 4,289 • 1992–1995 • Multiple centers in the United States	• Nonsmokers: Never smoked regularly • Quit before pregnancy: Quit before last menstrual period and validated with cotinine mid-pregnancy • Quit during pregnancy: Quit after last menstrual period and validated with cotinine mid-pregnancy • Quit before/during pregnancy: Women from two previous categories combined • Continued smoking: Smoking at study enrollment • Smoking status based on self-reports obtained at study enrollment • (13–21 weeks' gestation) • Quit status validated with urine cotinine concentration obtained mid-pregnancy (mean: 28 weeks' gestation)	**Mean adjusted birth weight (SE) and difference in mean adjusted birth weight:** • Nonsmokers: 3,232 g (12.3 g) (reference) • Quit before or during pregnancy, self-report: 3,233 g (17.7 g), +1 g • Quit before or during pregnancy, cotinine validated: 3,253 g (19.3 g), +21 g • Continued smoking: 3,071 g (19.1 g), -161 g, p <0.05	Results adjusted for maternal BMI, race, study center, sex of the infant, and gestational age Did not account for alcohol or illicit drug use
Abrevaya et al. (2008)	• Analysis of linked certificates of live births • First and second singleton pregnancies in which women smoked during the first pregnancy • n = 22,775 • 1989–2004 • Michigan	• Quit smoking between pregnancies: Smoked during the first pregnancy but not during the second pregnancy • Continued smoking during both pregnancies: Smoked during first and second pregnancies • Smoking status based on smoking history collected from certificates of live births, which used one question on tobacco use during pregnancy (yes/no)	**Mean adjusted birth weight (SD) and difference in mean adjusted birth weight (95% CI):** • 18–24 years of age: – Quit: 3,258 g (545 g) (reference) – Continued smoking: -134 g (-152– -115 g) • 25–30 years of age: – Quit: 3,317 g (536 g) (reference) – Continued smoking: -115 g (-138– -92 g)	Results adjusted for maternal race, education, income, population, interpregnancy interval, year of birth, trimester of first prenatal visit, presence of father's name on birth certificate, number of prenatal visits, and first-birth value of the outcome Did not account for alcohol or illicit substance use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Mendez et al. (2008)	• Prospective cohort study of childhood overweight • Term births • n = 482 • 1997–1998 • Spain	• Nonsmokers: Never smoked • Quit smoking before pregnancy • Quit smoking during the first trimester • Continued smoking: Still smoking during the second trimester • Smoking status based on self-reports	**Mean unadjusted birth weight (SD) and difference in mean adjusted birth weight:** • Nonsmokers/quit smoking before pregnancy: 3,282 g (442 g) • Quit smoking during the first trimester: 3,259 g (417 g), +23 g • Continued smoking: 3,085 g (430 g), -197 g, p <0.05 compared with nonsmokers/women who quit smoking before pregnancy	Analysis restricted to term births Results not adjusted for potential confounders Did not account for alcohol or illicit drug use
Nijiati et al. (2008)	• Prospective cohort study • Singleton births • n = 939 • 2006 • Hiroshima, Japan	• Nonsmokers: Did not smoke before or during pregnancy • Quit smoking: Quit during pregnancy • Continued smoking: Smoked before and continued smoking during pregnancy • Smoking status based on self-reports ascertained by questionnaire • Did not describe when questionnaire was administered, when women quit smoking, and procedures for follow-up and outcomes ascertainment	**Mean birth weight (SD) and difference in mean birth weight:** • Nonsmokers: – Unadjusted: 3,075 g (368 g) (reference) – Adjusted 3,241 g (377 g) (reference) • Quit smoking: – Unadjusted: 3,043 g (421 g), -32 g – Adjusted: 3,197 g (377 g), -44 g • Continued smoking: – Unadjusted: 2,897 g (348 g), -178 g – Adjusted: 3,099 g (462 g), -142 g, p = 0.0004	Results adjusted for sex of the infant, parity, maternal age, mother's BMI and height, gestational age, and exposure to secondhand smoke during pregnancy Did not account for alcohol or illicit drug use
Sasaki (2008)	• Prospective cohort study of gene–environment interactions in women • Singleton pregnancies • Excluded women with pregnancy complications (hypertension, diabetes) • n = 460 • 2002–2005 • Sapporo, Japan	• Nonsmokers: Did not smoke during pregnancy • Quit smoking: Quit in the first trimester • Continuing smokers: Smoked after the first trimester • Smoking status based on self-reports ascertained from a questionnaire administered at study enrollment	**Mean unadjusted birth weight (SD) (Kruskal-Wallis test, p = 0.003) and difference in mean adjusted birth weight:** • Nonsmokers: 3,078 g (347 g) (reference) • Quit smoking: 3,138 g (384 g), -60 g • Continued smoking: 2,961 g (386 g), -117 g **Difference in mean adjusted birth weight:** • Nonsmokers (reference) • Quit smoking: -31 g • Continued smoking: -148 g	Results adjusted for maternal age, height, weight, gestational weight gain, alcohol use, parity, sex of the infant, gestational age, and income Did not account for illicit drug use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Andersen et al. (2009)	• Clinic-based study of endothelial function by smoking status • Term pregnancies without complications (diabetes, hypertension) • n = 266 • 2003–2004 • Denmark	• Nonsmoker: Did not smoke before pregnancy • Quit smoking: Smoked during pregnancy but quit by 18 weeks' gestation • Continued smoking: Smoked throughout pregnancy • Smoking status based on self-reports ascertained from questionnaire and validated with serum cotinine	**Mean unadjusted birth weight (95% CI) and difference in mean birth weight** • Nonsmoker: 3.65 kg (3.01–4.50 kg) (reference) • Quit smoking: 3.60 kg (3.06–4.55 kg), -0.05 kg • Continued smoking: 3.30 kg (2.54–4.14): – Unadjusted: -364 g – Adjusted: -242 g, p = 0.002	Analysis restricted to term births Birth weight difference for continued smoking vs. nonsmokers adjusted for endothelial nitric oxide synthase, pre-pregnancy BMI, parity, gestational age, and sex of the infant Did not account for alcohol or illicit drug use
Fasting et al. (2009)	• Prospective intervention • of allergy prevention • in children • n = 711 • 2000–2002 • Norway	• Nonsmoker: Not smoking when became pregnant • Quit smoking: Smoking when became pregnant but quit by enrollment • Continued smoking: Smoking when became pregnant and still smoking at enrollment • Smoking status based on self-reports collected at study enrollment (median gestational age 11 weeks, all <28 weeks)	**Mean birth weight (SD) and difference in mean birth weight:** • Nonsmoker: 3,646 g (518 g) (reference) • Quit smoking: 3,628 g (497 g), -14 g • Continued smoking: 3,449 g (486 g), -197 g	Results not adjusted for potential confounders Did not account for alcohol or illicit drug use Did not show direct statistical comparisons between groups
Johansson et al. (2009)	• Births from the Swedish Birth Registry • First and second consecutive, singleton pregnancies • n = 555,046 • 1983–2002 • Sweden	• Nonsmoker: Did not smoke during either pregnancy • Quit smoking: Smoked during first but not during second pregnancy • Started smoking: Smoked during second but not during first pregnancy • Continued smoking: Smoked during both pregnancies • Smoking status ascertained from Swedish Birth Registry, as derived from first antenatal visit, typically <15 weeks' gestation; no information on cessation during pregnancy	**Mean birth weight second pregnancy (SD) and difference in mean birth weight:** • First pregnancy for each exposure group (reference) • Nonsmoker: 3,658 g (535 g), +173 g • Quit smoking: 3,643 g (539 g), +233 g • Started smoking: 3,520 g (545 g), +80 g • Continued smoking: 3,430 g (539 g), +119 g	Quit status defined across pregnancies but not within pregnancies Results not adjusted for potential confounders Did not account for alcohol or substance use Did not show direct statistical comparisons between groups

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Kabir et al. (2009)	• Cross-sectional study of changes in smoking status after a workplace • Singleton, live births • n = 15,241 • 2003 and 2005 • Ireland	• Nonsmokers: Never smokers • Quit smoking: Former smokers • Continued smoking: Current smokers • Smoking status based on self-reports • No details of how and when smoking status was ascertained • Authors reported that smoking status across different periods of gestation was not available	**Mean adjusted birth weight (95% CI) and difference in mean adjusted birth weight:** • 2003: – Nonsmoker: 3,527 g (3,450–3,604 g) (reference) – Quit smoking: 3,549 g (3,435–3,663 g), +22 g – Continued smoking: 3250 g (3,157–3,343 g), -370 g • 2005: – Nonsmoker: 3,503 g (3,426–3,580 g) (reference) – Former smoker: 3,547 g (3,433–3,661 g), +44 g – Current smoker: 3,220 g (3,127–3,313 g), -283 g	Results adjusted for gestational age Results not adjusted for smoking ban other potential confounders Did not account for alcohol or substance use
McCowan et al. (2009)	• Prospective cohort study designed to develop screening tests for pregnancy complications • n = 2,504 • 2004–2007 • New Zealand and Australia	• Nonsmokers: Did not smoke during pregnancy • Quit smoking: Smoked during pregnancy but quit before being interviewed at • 15 weeks' gestation • Continued smoking: Smoked at 15 weeks' gestation • Smoking status based on self-reports ascertained at 15 weeks' gestation	**Mean adjusted birth weight (SD) and difference in mean adjusted birth weight:** • Nonsmoker: 3,409 (592 g) (reference) • Quit smoking: 3,479 g (560 g) +70 g • (-6–146 g), p = 0.09 • Continued smoking: 3,139 (751g) -270 g (-350– -190 g), p <0.001	Results adjusted for maternal age; ethnicity; marital status; employment; BMI; bleeding during pregnancy; folic acid use; multivitamin use; alcohol consumption at 15 weeks' gestation; and scores for depression, stress, or anxiety Did not account for illicit drug use
Adegboye et al. (2010)	• Retrospective cohort study of risk factors for postpartum weight retention • Singleton pregnancies • n = 1,753 • 1984–1985 • Sweden	• Nonsmokers: Never smoked • Quit smoking: Quit smoking during first trimester and remained abstinent throughout pregnancy • Continued smoking: Continued to smoke during pregnancy • Smoking status based on self-reports collected after delivery; details not reported	**Mean unadjusted birth weight (SD):** • Nonsmoker: 3.5 kg (0.5 kg) • Quit smoking: 3.4 kg (0.5 kg) • Continued smoking 3.3 kg (0.5 kg) • p <0.001	Results not adjusted for potential confounders Did not account for alcohol or substance use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Prabhu et al. (2010)	• Prospective cohort study of risk factors for childhood asthma and allergy • n = 1,924 • 1997–1999 • Scotland	• Nonsmoker: Never smoked or quit smoking before pregnancy (additional details related to timing of cessation not reported) • Quit smoking: Quit in first trimester • Continued smoking in first trimester: • No change in number of cigarettes/day • Reduced number of cigarettes/day • Smoking status based on self-reports obtained at enrollment in the first trimester and at 32 weeks' gestation	**Difference in mean adjusted birth weight (95% CI):** • Continued smoking, no change in number of cigarettes/day (reference) • Nonsmoker: +290 g (115–463 g) • Reduced number of cigarettes/day: +104 g (-73–282 g) • Quit smoking: +246 g (46–445 g)	Results adjusted for sex of the infant, maternal height, plasma alpha-tocopherol and cholesterol, paternal smoking, and gestational age Did not account for alcohol or substance use
Vardavas et al. (2010)	• Population-based cohort study • n = 1,400 • 2007–2008 • Crete, Greece	• Nonsmoker: Did not smoke from 3 months before and throughout pregnancy • Quit smoking: Stopped smoking between 3 months before pregnancy and 12 weeks' gestation • Continued smoking: Smoked at 12 weeks' gestation • Smoking status based on self-reports obtained at enrollment, second, and third trimesters	**Mean unadjusted birth weight (SD) and difference in mean adjusted birth weight (95% CI):** • Nonsmoker: 3,171 g (473 g) (reference) • Quit smoking: 3,207 g (465 g), +39 g (-18–96) • Continued smoking: 3,059 g (498 g), -119 g (-177– -62 g)	Results adjusted for gestational age, parity, origin (Greek/non-Greek), maternal education, age, and sex of the infant Did not account for alcohol or illicit drug use
Bakker et al. (2011)	• Population-based, prospective cohort study • n = 5,389 • 2001–2005 • Netherlands	• Nonsmokers: Did not smoke during pregnancy • Quit smoking: Smoked during pregnancy but only during first trimester • Continued smoking (categories collapsed for analysis): • Second trimester: Smoked during pregnancy and during second trimester • Third trimester: Smoked during pregnancy and during third trimester • Smoking status based on self-reports obtained in each trimester of pregnancy	**Mean birth weight (SD) and difference in mean birth weight (95% CI):** • Nonsmokers: 3,473 g (547 g) (reference) • Quit smoking: – Unadjusted: 3,418 g (555 g), -55 g, p <0.05 – Adjusted, single assessment: -14 g (-49–20 g) – Adjusted, repeated assessment of smoking status: +38 g (-3–79 g) • Continued smoking: – Unadjusted: 3,274 g (500 g), -199 g, p <0.01 – Adjusted, single assessment: -157 (-194-120 g) – Adjusted, repeated assessment of smoking status: -143 (-175– -111 g)	Results adjusted for maternal age, BMI, height, education, ethnicity, parity, alcohol consumption, caffeine intake, folic acid intake, maternal stress, gestational age at birth, and sex of the fetus Did not account for illicit drug use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Benjamin-Garner and Stotts (2013)	• Randomized trial of a behavioral intervention for smoking cessation • Term, singleton pregnancies • 2001–2004 • n = 260 • 2001–2004 • Texas	• Quit smoking: Salivary cotinine <15 ng/mL in late pregnancy (36 weeks' gestation) • Light smoker: Salivary cotinine <150 ng/mL at enrollment, continued smoking (stayed light or increased to heavy) • Heavy smoker: Salivary cotinine ≥150 ng/mL at enrollment, continued smoking (stayed heavy or decreased to light) • Smoking status based on self-report and salivary cotinine obtained at enrollment (16–26 weeks' gestation), 36 weeks' gestation, and 6 weeks postpartum	**Mean unadjusted birth weight (SD) and difference in mean unadjusted birth weight:** • Quit smoking: 3,415 g (521g) (reference) • Light smoker, stayed light: 3,252 g (504 g), -163 g • Light smoker, increased to heavy: 3,212 g (447 g), -203 g • Heavy smoker, decreased to light: 3,315 g (368 g), -100 g • Heavy smoker, stayed heavy: 3,116 g (447 g), 299 g • Pairwise comparison found that the only significant difference was between heavy smokers who stayed heavy smokers and quitters (p = 0.02). Findings did not change after adjustment for potential confounders (p = 0.05).	Randomized cessation trial, and thus no comparison group of nonsmokers Results adjusted for maternal age, race/ethnicity, parity, education, income, sex of the infant, gestational age at delivery, pre-pregnancy BMI, and gestational weight gain (education and parity removed from final models) Restricted to term births Did not account for alcohol or substance use
Himes et al. (2013)	• Prospective cohort study • Date not provided • n = 119 • Rhode Island	• Nonsmokers: Did not smoke during pregnancy • Quit smoking: Smoked during pregnancy but quit before delivery • Smoked throughout pregnancy • Smoking status throughout pregnancy based on self-reports obtained in third trimester of pregnancy, >28 weeks' gestation	**Mean unadjusted birth weight (SD) and difference in mean birth weight:** • Smokers: 3,162 g (434 g) (reference) • Nonsmokers: 3,464 g (444 g), +302 g • Quit smoking: 3,557 g (504 g), +395 g	Differences between continuing smokers and nonsmokers and quitters were statistically significant, even after adjusting for socioeconomic status, maternal age, income, and education (data not shown) Excluded women who used illicit drugs

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Juarez and Merlo (2013)	• Births from the Swedish Medical Birth Register • Singleton, term births • n = 677,922 births for conventional analysis • n = 62,941 siblings for sibling analysis • 2002–2010 • Sweden	• Nonsmokers: Not smoking at either early or late antenatal visit • Continued smoking: Smoking at early and late antenatal visits: – Light, light smoker – Light, heavy smoker – Heavy, light smoker – Heavy, heavy smoker • Quit smoking: Smoked at first but not second antenatal visit: – Light, quit smoking – Heavy, quit smoking • Started smoking: Did not smoke at first antenatal visit but smoked at second antenatal visit: – Nonsmoker, light smoker – Nonsmoker, heavy smoker • Light smokers: 1–9 cigarettes/day • Heavy smokers: ≥10 cigarettes/day • Smoking status obtained from the Swedish Medical Birth Register which relies on self-reported data collected during early (10–12 weeks' gestation) and late (30–32 weeks' gestation) antenatal visits	**Difference in mean adjusted birth weight (95% CI):** • Conventional analysis: – Nonsmokers (reference) – Quit smoking: ○ Light, quit: -47 g (-55– -40 g) ○ Heavy, quit: -79 g (-100– -58 g) – Continued smoking: ○ Heavy, heavy: -303 g (-313– -292 g) ○ Light, heavy: -265 g (-279– -250 g) ○ Heavy, light: -254 g (-266– -242 g) ○ Light, light: -221 g (-227– -214 g) ○ Started smoking: ○ Nonsmoker, light: -129 g (-142– -117 g) ○ Nonsmoker, heavy: -142 g (-177– -108 g) • Sibling analysis: – Nonsmokers (reference) – Quit smoking: ○ Light, quit: -29 g (-42– -16 g) ○ Heavy, quit: -1 g (-46– –44 g) – Continued smoking: ○ Heavy, heavy: -226 g (-274– -179 g) ○ Light, heavy: -259 g (-309– -209 g) ○ Heavy, light: -194 g (-238– -151 g) ○ Light, light: -162 g (-178– -147 g) – Started smoking: ○ Nonsmoker, light: -77 g (-97– -57 g) ○ Nonsmoker, heavy: -83 g (-140– -25 g) – Effects of smoking on birth weight were attenuated by 6–78 g using sibling analysis compared with traditional analysis	Results adjusted for gestational age, marital status, maternal age, birth order, sex of the newborn, pregnancy complications (diabetes, hypertension, urinary problems), and use of snus Did not account for alcohol or substance use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Miyake et al. (2013)	• Prospective cohort study • n = 1,565 • 2007–2008 • Japan	• Nonsmoker: Did not smoke during pregnancy • Quit smoking: • First trimester: Smoked during first trimester only • Second or third trimester: Smoked during second or third trimester but not throughout pregnancy • Continued smoking: Smoked throughout pregnancy • Smoking status for each trimester of pregnancy based on self-reports obtained after delivery	**Mean adjusted birth weight (95% CI) and difference in mean adjusted birth weight:** • Nonsmoker: 3,011 g (2,994, 3,027) (reference) • Quit smoking first trimester: 3,028 g (2,951–3,104 g), +17 g • Quit smoking second or third trimester: 2,958 g (2,838–3,079 g), -53 g • Continued smoking: 2,841 g (2,738–2,944 g), -170 g • p for trend = 0.005	Results adjusted for maternal age, residence, education, employment, alcohol consumption, and BMI; family structure; gestational age at birth; and sex of the infant Did not address illicit drug use
Murphy et al. (2013)	• Prospective cohort study • Singleton pregnancies • n = 1,216 • 2010–2011 • Dublin, Ireland	• Nonsmoker: Not defined • Quit smoking: Smoked during 6 months before pregnancy but quit by first prenatal visit • Continued smoking: Smoked during 6 months before pregnancy, at first prenatal visit, and during third trimester • Smoking status based on self-reports obtained at enrollment and third trimester	**Mean birth weight (SD) and difference in mean adjusted birth weight (95% CI):** • Nonsmoker: 3,496 g (509 g) (reference) • Quit smoking: 3,503 (491 g), +7 g (-81–95 g) • Continued smoking: 3,305 g (491 g), -191 g (-194– -88 g)	Results adjusted for maternal age, BMI, nationality, unplanned pregnancy, private healthcare, alcohol use, and illicit drug use
Rode et al. (2013)	• Prospective cohort study • Singleton, term pregnancies • n = 1,774 • 1996–1999 • Copenhagen, Denmark	• Nonsmokers: Not defined • Quit smoking: Quit smoking immediately before or during pregnancy • Continued smoking: Not defined • Smoking status based on self-reports and on salivary cotinine obtained in a subgroup at 16 and 37 weeks' gestation • Smoking status assessed at 12–18 weeks' gestation, 37 weeks' gestation, and • 1 year postpartum	**Mean birth weight (SD) and difference in mean birth weight (95% CI):** • Nonsmokers: 3,675 g (482 g) (reference) • Quit: 3,670 g (510 g) – Unadjusted difference: +4 g (-66–64 g) – Adjusted difference: +26 g (-29–81 g) • Continued smoking: 3,405 g (487 g) – Unadjusted difference: -270 g (-333– -208 g) – Adjusted difference: -260 g (-318– -204 g)	Results adjusted for pre-pregnancy BMI, gestational age, and parity Restricted to term births Did not account for alcohol or substance use Salivary cotinine for subgroup reported but not integrated into main analysis

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Meghea et al. (2014)	• Prospective cohort study • n = 474 • 2008–2009 • Romania	• Nonsmokers: Not smoking when learned of pregnancy • Quit smoking: Quit upon learning of pregnancy • Continued smoking: Smoking at time of study interview (gestational age not reported) • Smoking history based on self-reports obtained at study enrollment (gestational age not reported)	**Mean unadjusted birth weight and difference in mean birth weight:** • Nonsmoker: 3382 g (reference) • Quit smoking: 3340 g – Unadjusted: -42 g – Adjusted: -48 g • Continued smoking: 3176 g – Unadjusted: -206 g, p <0.05 – Adjusted: -165 g	Results adjusted for stress, depressive symptoms, maternal age >35 years old, education, rural residence, marital status, and nulliparity Did not account for alcohol or substance use
Räisänen et al. (2014)	• Finnish Medical Birth Register • Singleton deliveries, live or stillborn • n = 1,164,953 • 1991–2010 • Finland	• Nonsmokers: Not defined • Quitters: Quit smoking during first trimester • Continuing smokers: Smoked after first trimester • Smoking history ascertained from the Finnish Medical Birth Register	**Mean unadjusted birth weight (SD) and difference in mean birth weight:** • Nonsmokers: 3,575 g (547 g) (reference) • Quitters: 3,531 g (546 g), -44 g • Continuing smokers: 3,383 g (586 g), -192 g	Results not adjusted for potential confounders Results of statistical testing not provided. Did not account for alcohol or substance use
Slatter et al. (2014)	• Study of smoking and placental pathology • Singleton, term births • Excluded women with diabetes or hypertension • n = 236 • 2009–2011 • New Zealand	• Nonsmokers: Did not smoke during pregnancy • Quit smoking: Stopped smoking at least 4 weeks before delivery • Continued smoking: Smoked during pregnancy and up to delivery • Smoking history based on self-reports obtained at the time placentas were collected	**Mean unadjusted birth weight (SD) and difference in mean adjusted birth weight:** • Nonsmokers: 3.56 kg (0.36 kg) • Quit smoking: 3.64 kg (0.59 kg), +0.08 kg • Continuing smokers: 3.29 kg (0.49 kg), -0.27 kg	Results not adjusted for potential confounders, but restricted to term births Did not account for alcohol or substance use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Suzuki et al. (2014)	• Prospective cohort study • Singleton deliveries • 1991–2006 • n = 2,663 • Japan	• Nonsmokers: Never smoked • Quit smoking before pregnancy • Quit smoking during early pregnancy • Continued smoking: Smoking at study enrollment • Smoking exposure categories not further defined • Smoking history based on self-reports obtained during early pregnancy (usually first trimester)	**Mean unadjusted birth weight (SD):** • Nonsmokers: 3,069 g (387 g) • Quit before pregnancy: 3,052 g (393 g) • Quit during early pregnancy: 3,046 g (409 g) • Continued smoking: 2,902 g (409 g) **Mean adjusted birth weight and difference in mean adjusted birth weight, by sex:** • Boys: – Nonsmokers: 3,084 g (reference) – Quit smoking before pregnancy: 3,015 g, 69 g, p = 0.2 – Quit smoking during early pregnancy: 3,065 g, -19 g, p = 0.9 – Continued smoking: 2,960 g, -124 g, p = 0.002 • Girls: – Nonsmokers: 3,039 g (reference) – Quit smoking before pregnancy: 3,029 g, 10 g, p = 0.99 – Quit smoking during early pregnancy: 3,063 g, +24 g, p = 0.8 – Continued smoking: 2,888 g, -151 g, p = 0.002	Results adjusted for maternal age, parity, BMI, and gestational age Did not account for alcohol or substance use
Bailey (2015)	• Randomized clinical trial of smoking cessation intervention • n = 1,486 • 2008–2012 • Tennessee	• Quit smoking: Smoked at first prenatal visit but quit by third trimester • Continued smoking: Smoked at first prenatal visit and still smoking in the third trimester • Smoking history based on self-reports obtained at first prenatal visit • Quit status ascertained in third trimester by exhaled CO, urine cotinine, and self-report at delivery	**Mean adjusted birth weight and difference in mean adjusted birth weight:** • Quit smoking: 3,216 g, +204 g • Continued smoking: 3,012 g (reference) • p <0.001	Randomized cessation trial and thus no comparison group of nonsmokers Results adjusted for maternal age, education, marital status, insurance status, and marijuana use Examined alcohol use, but it was not significant in the model

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Blatt et al. (2015)	• Population-based retrospective cohort study using Ohio certificates of live birth • n = 927,424 • 2006–2012 • Ohio	• Nonsmoker: Did not smoke during 3 months before pregnancy or during pregnancy • Quit smoking before pregnancy: Smoked during 3 months before pregnancy but not during pregnancy • Quit smoking, first trimester: Smoked during first trimester only • Quit smoking, second trimester: Smoked during first and second trimesters, but not third trimester • Continued smoking: Smoked throughout pregnancy • Smoking history ascertained from vital statistics data and certificates of live birth	**Mean birth weight (SD) and difference in mean birth weight:** • Nonsmokers: 3,340 g (558 g) (reference) • Quit smoking before pregnancy: 3,339 g (557 g), -1 g • Quit smoking, first trimester: 3,280 g (590 g), -60 g • Quit smoking, second trimester: 3,072 g (763 g), -268 g • Continued smoking: 3,090 g (542), -250 g	Results not adjusted for potential confounders Statistical testing not reported Did not account for alcohol or substance use
Grzeskowiak et al. (2015)	• Retrospective cohort study • n = 7,658 • 2000–2005 • South Australia	• Nonsmokers • Quit smoking during pregnancy • Continued smoking: Smoked during pregnancy • Smoking status not further defined • Smoking history based on self-reports ascertained at first prenatal care visit	**Mean birth weight (SD) and difference in mean birth weight:** • Nonsmokers: 3,410 g (610 g) (reference) • Quit smoking: 3,408 g (608 g) (-2 g) • Continuing smokers 3,155 g (628 g), -255 g, p <0.001	Results not adjusted for potential confounders Did not account for alcohol or substance use
Yan and Groothuis (2015)	• Population-based cohort study • Singleton pregnancies • Excluded women with chronic diseases • n = 11,131 • 2000–2001 • United Kingdom	• Nonsmokers: Not defined • Quit smoking before pregnancy (timing of cessation not specified) • Quit smoking during pregnancy (month of cessation noted) • Continued smoking: Smoked beyond 7 months' gestation • Smoking history based on self-reports ascertained when infants were 9 months old	**Mean unadjusted birth weight (SD) and difference in mean birth weight:** • Nonsmokers 3,452 g (551 g) • Quit smoking before pregnancy: -8 g • Quit smoking month 1: -5 g • Quit smoking month 2: -5 g • Quit smoking month 3: -9 g • Quit smoking month 4: -143 g, p <0.05 • Quit smoking month 5: -170 g, p <0.05 • Quit smoking month 6: -184 g • Quit smoking month 7: -215 g, p <0.05 • Continued smoking: -245 g, p <0.05 • Quit smoking trimester 1: -5 g • Quit smoking trimester 2: -159 g, p <0.05 • Continued smoking: -245 g, p <0.05	Results adjusted for birth year/quarter of infant, maternal weight, height, income, prenatal care initiation, alcohol use, maternal employment status, home satisfaction, religion affiliation, and racist or religion-based insults in living area Did not account for substance use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Hayes et al. (2016)	• Quasi-experimental, historical cohort of smoking cessation intervention trial • Excluded deliveries of infants <1,500 g • n = 652 • 2004–2005 • Ireland	• Quit smoking before enrollment: Smoked when became pregnant, quit before first study visit, and did not resume smoking • Quit smoking after enrollment: Smoked at time of first study visit but quit by third study visit (combined with "attempted to quit" for adjusted analysis) • Attempted to quit: Attempted to quit at first or second study visit but resumed at one or more visits (combined with "quit smoking after enrollment" for adjusted analysis) • Continued smoking: Smoked at the time of all three study visits • Smoking status based on self-reports and validated with urine cotinine levels at second study visit (did not describe how cotinine levels were used in the analysis), and ascertained at three visits (12–18 weeks' gestation, 28–32 weeks' gestation, and within 1 week of delivery)	**Median birth weight and difference in mean birth weight (95% CI):** • Quit smoking before enrollment: 3,600 g, 3,595 g (reference) • Quit smoking after enrollment: 3,340 g, p = 0.07 • Attempted to quit: 3,450 g, p = 0.13 • Continued smoking: 3,260 g, 3,269 g, -326 g (-483– -17), p < 0.01 **Difference in mean adjusted birth weight (95% CI):** • All: – Continued smoking (reference) – Quit smoking before enrollment: +288 g (153–423 g) – Quit smoking after enrollment or attempted to quit: +147 g (50–244 g) • Preterm: – Continued smoking (reference) – Quit smoking before enrollment: +67 g (-272–407 g) – Quit smoking after enrollment or attempted to quit: +181 g (-236–600 g) • Term: – Continued smoking (reference) – Quit smoking before enrollment: +327 g (183–472 g) – Quit smoking after enrollment or attempted to quit: +146 g (46–246 g)	Randomized cessation trial and thus no comparison group of never smokers Results adjusted for other smokers in the household, gestational age at delivery, and sex of infant Did not account for alcohol or substance use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
Suzuki et al. (2016) (continues on next page)	• Population-based cohort study • Singleton pregnancies • n = 7,734 • 2011–2014 • Japan	• Nonsmokers: Never smoked • Quit smoking before pregnancy: Not further defined • Quit smoking during early pregnancy: Not further defined • Continued smoking: Currently smoking at time in which study questionnaire was administered • Smoking status based on self-reports collected in second trimester	**Mean birth weights (SD) and difference in mean birth weight:** • Nonsmokers: 3,015 g (427 g) (reference) • Quit smoking before pregnancy: 3,029 g (408 g), +14 g • Quit smoking during early pregnancy: 3,011 g (444 g), -4 g • Continued smoking: 2,873 g (423 g), -142 g **Mean adjusted birth weights (SE) and difference in mean adjusted birth weight by sex of newborn:** • Female: – Nonsmokers: 3,018 g (16 g) (reference) – Quit smoking before pregnancy: 3,030 g (18 g), +12 g, p = 0.7 – Quit smoking during early pregnancy: 2,979 g (21 g), -39 g, p = 0.06 – Continued smoking: 2,894 (28 g), -124 g, p <0.001 • Male: – Nonsmokers: 3,096 g (17 g) (reference) – Quit before pregnancy: 3,089 g (18 g), -7 g, p = 0.9 – Quit during early pregnancy: 3,068 g (20 g), -28 g, p = 0.2 – Continued smoking: 2,960 g (27 g), -136 g, p <0.001 • Term births—Female: – Nonsmokers: 3,056 g (16 g) (reference) – Quit before pregnancy: 3,069 g (19 g), +13, p = 0.6 – Quit during early pregnancy: 3,021 g (21 g), -35 g, p = 0.1 – Continued smoking: 2,928 g (28 g), -128 g, p <0.001	Results adjusted for partner's smoking status, income, birth order, pregnancy complications (hypertension, diabetes), pre-pregnancy weight, gestational weight gain, maternal age, and gestational age Results stratified by term/preterm delivery Did not account for alcohol or substance use

Table 4.32 Continued

Study	Design/population	Exposure groups/how determined	Estimate of effects	Comments
(continued from previous page) Suzuki et al. (2016)	—	—	• Term births—Male: – Nonsmokers 3,142 g (18 g) (reference) – Quit before pregnancy: 3,134 g (19 g), +8 g, p = 0.9 – Quit during early pregnancy: 3,110 g (21 g), -32 g, p = 0.2 – Continued smoking: 3,005 g (28 g), -137 g, p <0.001	—
Wallace et al. (2017) (reanalysis of Blatt et al. [2015])	• Population-based retrospective cohort study using Ohio certificates of live birth • Singleton pregnancies • Excluded congenital malformations • All participants had at least one previous preterm delivery • n = 36,432 • 2006–2012 • Ohio	• Nonsmoker: Did not smoke during 3 months before pregnancy or during pregnancy • Quit smoking by first trimester: Smoked during 3 months before pregnancy but not during pregnancy • Quit by second trimester: Smoked during first trimester but not during second and third trimesters • Quit by third trimester: Smoked during second trimester but not during third trimester • Continued smoking: Smoked during all three trimesters • Smoking status obtained from U.S. certificates of live birth	**Mean birth weight (SD) and difference in birth weight:** • Nonsmokers: 2,964 g (764 g) (reference) • Quit smoking by first trimester: 2,951 g (745 g), -13 g • Quit smoking by second trimester: 2,841 g (819 g), -123 g • Quit smoking by third trimester: 2,343 g (1,061 g), -621 g • Continued smoking: 2,743 g (667 g), -221 g • All comparisons significant at p <0.01	Results not adjusted for confounders Did not account for alcohol or substance use

Notes: **BMI =** body mass index; **CI =** confidence interval; **CO =** carbon monoxide; **g =** grams; **kg =** kilograms; **ng/mL =** nanograms per milliliter; **SD =** standard deviation; **SE =** standard error.

221 and 303 g in the conventional analysis for light and heavy smokers, respectively. Also, in the sibling analysis, cessation was associated with a reduction in birth weight of 29 g (95% CI, -42 to -16) for light smokers compared with nonsmokers, but it was not associated with a significant reduction in birth weight in heavy smokers (-1 g; 95% CI, -46–44). By comparison, using nonsibling controls, babies of light smokers who quit had a reduction in birth weight of 47 g (95% CI, -55 to -40), while heavy smokers who quit had a reduction of 79 g (95% CI, -100 to -58) compared with nonsmokers during pregnancy.

Several of the studies published since the 1990 and 2004 Surgeon General's reports examined the specific timing of tobacco smoke exposure and fetal growth. Yan and Groothuis (2015), who examined birth outcomes in more than 11,000 women and 2,000 smokers by gestational month of cessation through month 7, found little effect of smoking on birth weight in the first 3 months of pregnancy but increasing effects for every month women smoked after that. Estimates of the effect of smoking on birth weight were adjusted for several socioeconomic factors and alcohol use but not for gestational age, and they were statistically significant for months 4, 5, and 7. However, cessation status was not biochemically validated. Elsewhere, Blatt and colleagues (2015) examined cessation in a cohort of more than 900,000 births by trimester in a study using Ohio birth certificate data. Those researchers found a greater reduction in birth weight in quitters compared with nonsmokers over time (-60 g for smoking in the first trimester only, -268 g for smoking in the second trimester) but no further reduction for smoking through the third trimester (-250 g). The results were not adjusted for potential confounders or for gestational age, however, and there was no biochemical validation of cessation. All comparisons were statistically significant.

Two studies examined smoking patterns across pregnancies and, thus, focused on cessation between pregnancies rather than on cessation during pregnancies. Abrevaya (2008) found that, after stratifying results by age, both the younger (18–24 years of age) and older (25–30 years of age) groups of continuing smokers had babies with lower mean birth weights compared with quitters, even after adjusting for multiple potential confounders (-134 g and -115 g, respectively) (Abrevaya 2008). In Sweden, Johansson and colleagues (2009) assessed smoking status during antenatal care for mothers having two live births, comparing the outcomes of the second pregnancy within exposure groups with those for the first pregnancy, and found increases in birth weight of the babies of quitters (233 g) and nonsmokers (173 g) that exceeded the increase in continuing smokers (119 g). An important limitation of study designs that examine outcomes across consecutive pregnancies is that the smoking exposure categories are often simplified (e.g., assessing smoking at only one time point for each pregnancy). If the timing of cessation (such as during pregnancy rather than before pregnancy, or during a specific trimester of pregnancy) affects infant birth weight, the effect may not be detected in studies with limited assessment of smoking exposure.

Summary of the Evidence. Since the 2004 Surgeon General's report confirmed that smoking cessation eliminates much of the reduction in birth weight caused by maternal smoking (USDHHS 2004), numerous studies have assessed the relationships between smoking and smoking cessation and fetal growth. Many studies adjusted for multiple confounders, and some included biochemical validation of quit status. The evidence is sufficient to infer that smoking cessation during pregnancy reduces the effects of smoking on birth weight and gestational-age adjusted birth weight. Depending on the timing of cessation, the birth weight of infants of women who quit smoking before or in early pregnancy approached or met that of nonsmokers in many studies. The evidence is inadequate to infer the exact gestational age before which cessation should occur to eliminate the effects of smoking on birth weight or gestational-age adjusted birth weight.

Small for Gestational Age

In addition to gestational age–adjusted birth weight or birth weight in term infants, the designation of SGA (a birth weight ≤10th percentile for gestational age) or the infant's SGA status can be used as an indicator of fetal growth. SGA is a less sensitive measure of fetal growth than gestational age–adjusted birth weight, but it is strongly associated with increased morbidity and mortality (Pallotto and Kilbride 2006; Katz et al. 2013). The association between smoking-related reduction in birth weight and infant mortality has been studied in detail, as reviewed in the 2014 Surgeon General's report (USDHHS 2014).

Table 4.33 presents studies published after the year 2000 that addressed smoking cessation and SGA infants. Twenty-two studies were identified. Definitions for SGA included, by percentile of birth weight, less than the 2.5th, 3rd, 5th, and 10th percentiles; they also included greater than 2 standard deviations (SD) below the mean. All of the studies but one (Grzeskowiak et al. 2015) included adjustments for potential confounders; three also adjusted for alcohol consumption but not substance use (McCowan et al. 2009; Bakker et al. 2011; Tong et al. 2017); and two addressed both alcohol consumption and substance use (Erickson and Arbour 2012; Murphy et al. 2013). Two studies examined smoking status across two consecutive pregnancies (Okah et al. 2007; Kvalvik et al. 2017), and 20 examined cessation with respect to single pregnancies. Of those 20 studies, 19 compared infants of women who quit smoking with those of nonsmokers

Table 4.33 Studies on smoking cessation and small for gestational age infants

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Mitchell et al. (2002)	• Case-control • Term births without congenital anomalies • n = 1,714 • 1995–1997 • New Zealand	• Nonsmokers: Never smoked cigarettes regularly, or did not smoke during 12 months before pregnancy or during pregnancy • Quit smoking before pregnancy: Smoked during 12 months before pregnancy but not during pregnancy • Quit smoking during pregnancy • Continued smoking during pregnancy, increased amount • Continued smoking during pregnancy, decreased amount • Continued smoking during pregnancy, amount did not change • Smoking status based on self-reports obtained from a postpartum interview	<10th percentile for sex	**Unadjusted and adjusted ORs for SGA (95% CI):** • Nonsmokers (reference) • Quit smoking before pregnancy: – Unadjusted: 0.83 (0.55–1.27) – Adjusted: 1.03 (0.64–1.64) • Quit smoking during pregnancy: – Unadjusted: 1.13 (0.73–1.75) – Adjusted: 1.14 (0.68–1.91) • Continued smoking during pregnancy, increased amount: – Unadjusted: 1.94 (1.02–3.67) – Adjusted: 2.07 (0.97–4.42) • Continued smoking during pregnancy, decreased amount: – Unadjusted: 2.56 (1.86–3.52) – Adjusted: 3.23 (2.14–4.86) • Continued smoking during pregnancy, amount did not change: – Unadjusted: 3.35 (1.98–5.66) – Adjusted: 4.88 (2.66–8.94)	Results adjusted for maternal education, occupation, marital status, ethnicity, parity, age, age at first pregnancy, height, pre-pregnancy weight, hypertension, and marijuana use
England et al. (2007)	• Randomized trial for preeclampsia prevention • n = 4,289 • 1992–1995 • United States	• Nonsmokers: Never smoked regularly • Quit before pregnancy: Quit before last menstrual period and validated with cotinine mid-pregnancy • Quit during pregnancy: Quit after last menstrual period and validated with cotinine mid-pregnancy • Quit before or during pregnancy: Quit groups from two previous categories combined • Continued smoking: Smoking at study enrollment • Smoking status based on self-reports obtained at study enrollment (13–21 weeks' gestation) in 2007 study • Quit status validated with urine cotinine concentration obtained mid-pregnancy (mean: 28 weeks' gestation)	≤10th percentile for race, sex, and parity	**Unadjusted and adjusted OR (95% CI):** • Nonsmoker (reference) • Quit before or during pregnancy: – Unadjusted: 1.0 (0.7–1.4) – Adjusted: 1.0 (0.7–1.5) • Continued smoking: – Unadjusted: 1.9 (1.5–2.4) – Adjusted: 2.0 (1.6, 2.7)	Results adjusted for maternal BMI and study center Did not account for alcohol or substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Okah et al. (2007)	• Population-based retrospective cohort study using certificates of live births in Missouri • First and second singleton live births • n = 5,107 • 1994–2003 • Missouri	• Nonsmokers: Smoked during neither pregnancy • Smoked during first but not during second pregnancy • Smoked during second but not during first pregnancy • Smoked during both pregnancies • Smoking history ascertained from vital statistics data and certificates of live births, which used one question on tobacco use during pregnancy (yes/no)	<10th percentile for gestational age	**Adjusted OR for SGA in second pregnancy (95% CI):** • Nonsmoker (reference) • Smoked during first but not during second pregnancy: 1.31 (0.65–2.65) • Smoked during second but not during first pregnancy: 1.83 (1.19–2.82) • Smoked during both pregnancies: 2.80 (2.00–3.93)	Results adjusted for maternal age, race, and medical risk for SGA Did not account for alcohol or substance use
Pipkin (2008)	• Prospective cohort study of the genetics of preeclampsia • Singleton pregnancies with moderate to severe preeclampsia • n = 1,001 • Years: Not reported • United Kingdom	• Nonsmoker: Never smoked • Quit smoking: Quit before first antenatal visit but quit time not reported • Continued smoking: Smoking at the time of antenatal booking • Smoking status based on self-reports obtained at antenatal booking	<3rd percentile for gestational age	**Percentage SGA and adjusted OR for SGA (95% CI):** • Nonsmoker: 27.9% (reference) • Quit smoking: 37.5% • Continued smoking: 46.1%; 2.20 (1.41–3.44)	Results adjusted for maternal parity and BMI and sex of the infant
McCowan et al. (2009)	• Prospective cohort study • n = 2,504 • 2004–2007 • New Zealand and Australia	• Nonsmoker: Did not smoke during pregnancy • Quit smoking: Smoked during pregnancy but quit before being interviewed at 15 weeks' gestation • Continued smoking: Smoking at 15 weeks' gestation • Smoking status based on self-reports ascertained at 15 weeks' gestation	SGA birth weight <10th customized centile	**Adjusted OR (95% CI):** • Nonsmoker (reference) • Quit smoking: 1.06 (0.67–1.68) • Continued smoking: 1.76 (1.03–3.02)	Results adjusted for maternal age; ethnicity; marital status; employment status; BMI; bleeding during pregnancy; folic acid use; multivitamin use; alcohol use at 15 weeks' gestation; and scores for depression, stress, or anxiety Did not account for substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Polakowski et al. (2009)	• Population-based retrospective cohort using certificates live births • Singleton pregnancies >28 weeks' gestation • n = 915,441 • 2005 • Multiple sites in the United States	• Nonsmoker: Did not smoke during any trimester of pregnancy • Quit smoking, first trimester: Smoked during first trimester but not during second and third trimesters • Quit smoking, second trimester: Smoked during second trimester but not during third trimester • Continued smoking: Smoked during all three trimesters • Excluded women who did not fit any of the categories above • Smoking history ascertained from vital statistics data and certificates of live births	Birth weight <10th percentile weight for gestational age	**Adjusted OR for SGA (95% CI):** • Term (≥37 completed weeks): – Continued smoking (reference) – Nonsmokers: 0.41 (0.40–0.42) – Quit smoking, first trimester: 0.45 (0.42–0.48) – Quit smoking, second trimester: 0.59 (0.54–0.64) • Preterm (28–36 completed weeks): – Continued smoking (reference) – Nonsmokers: 0.45 (0.42–0.47) – Quit smoking, first trimester: 0.47 (0.40–0.55) – Quit smoking, second trimester: 0.88 (0.72–1.08)	Results adjusted for maternal age, race/ethnicity, marital status, education, late entry into prenatal care, and history of preterm delivery Did not account for alcohol or substance use
Vardavas et al. (2010)	• Population-based, prospective cohort study • Singleton pregnancies • n = 1,400 • 2007–2008 • Crete, Greece	• Nonsmoker: Did not smoke from 3 months before pregnancy through pregnancy • Quit smoking: Stopped smoking sometime between 3 months before pregnancy and 12 weeks' gestation. • Continued smoking: Smoking at 12 weeks' gestation • Smoking status based on self-reports obtained at enrollment and during second and third trimesters	Birthweight <10th percentile for gestational age	**Unadjusted OR for SGA (95% CI):** • Nonsmoker (reference) • Quit smoking: 0.73 (0.34–1.59) • Continued smoker: 2.36 (1.42–3.93) **Adjusted OR for SGA (95% CI):** • Nonsmoker (reference) • Quit smoking: 0.74 (0.34–1.62) • Continued smoker: 2.63 (1.55–4.49)	Results adjusted for origin, parity, maternal education, and age and sex of the infant Did not account for alcohol or substance use
Bakker et al. (2011)	• Population-based, prospective cohort study • n = 5389 • 2001–2005 • Netherlands	• Nonsmokers: Did not smoke during pregnancy • Quit smoking, first trimester: Smoked only during first trimester • Quit smoking, second trimester: Smoked during second trimester (combined with "continued smoking" for this analysis) • Continued smoking: smoked during third trimester (combined with "quit smoking, second trimester" for this analysis) • Smoking status based on self-reports obtained in each trimester of pregnancy	Birth weight <5th percentile for gestational age	**Adjusted OR for SGA (95% CI):** • Nonsmokers (reference) • Quit smoking: 1.17 (0.73–1.88) • Continued smoking 2.11 (1.55–2.88)	Results adjusted for maternal age, BMI, height, education, ethnicity, parity, alcohol consumption, caffeine intake, folic acid intake, maternal stress, gestational age at birth; and sex of the fetus Did not account for substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Baba et al. (2012)	• Population-based cohort study based on Swedish Medical Birth Register • Singleton pregnancies • n = 846,411 • 1999–2010 • Sweden	• Nonusers: Did not use snuff or smoke cigarettes before pregnancy or during early pregnancy (≤15 weeks' gestation) • Quit smoking, early: Smoked before pregnancy but quit during early pregnancy • Continued smoking, early: Smoked before and during early pregnancy (based on first assessment of smoking status at ≤15 weeks' gestation) • Quit smoking, late: Smoked during early pregnancy but not during late pregnancy (based on assessment of smoking status at ≤15 weeks' gestation and 30–32 weeks' gestation) • Continued smoking: Smoked during early and late pregnancy • Smoking status based on self-reports assessed at first antenatal visit (typically ≤15 weeks' gestation) and again in late pregnancy (typically 30–32 weeks' gestation)	Birth weight >2 SD below the mean for gestational age using sex-specific growth curves	**Unadjusted and adjusted OR for SGA (95% CI):** • Based on early assessment: – Nonuser (reference) – Quit smoking, early: ○ Unadjusted: 1.17 (1.11–1.24) ○ Adjusted: 1.03 (0.98–1.09) – Continued smoking, early: ○ Unadjusted: 2.69 (2.58–2.80) ○ Adjusted: 2.55 (2.43–2.67) • Based on late assessment: – Nonuser (reference) – Quit smoking, late: ○ Unadjusted: 2.01 (1.83–2.21) ○ Adjusted: 1.82 (1.65–2.01) – Continued smoking, late: ○ Unadjusted: 3.18 (3.01–3.36) ○ Adjusted: 3.21 (3.02–3.40) **Adjusted OR for preterm SGA and term SGA (95% CI):** • Nonuser (reference) • Quit smoking, early: – Preterm SGA: 0.86 (0.76–0.98) – Term SGA: 1.07 (1.01–1.14) • Continued smoking, early: – Preterm SGA: 1.85 (1.67–2.06) – Term SGA: 2.76 (2.62–2.91)	Results adjusted for maternal age, parity, education, early pregnancy BMI, cohabitation, height, pregestational diabetes, and essential hypertension Did not account for alcohol or substance use
Bickerstaff et al. (2012)	• Retrospective cohort • n = 30,524 • 1997–2006 • Australia	• Nonsmokers: Never smoked or quit >12 months before booking • Quit smoking: Smoked during 12 months before booking but quit before booking • Continuing smokers: Currently smoking at booking • Smoking status based on routinely collected clinical data	<10th and <3rd percentiles using customized centiles for Australian ethnicities	**Adjusted OR for SGA (95% CI):** • 10th percentile: – Continuing smokers vs. nonsmokers: 2.26 (2.08–2.47) – Quit smoking vs. continuing smokers: 0.43 (0.33–0.57) • 3rd percentile: – Continuing smokers vs. nonsmokers: 2.41 (2.14–2.73) – Quit smoking vs. continuing smokers: 0.46 (0.31–0.68)	Results adjusted for plurality, previous pregnancy complications, parity, and ethnicity Did not account for alcohol or substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Erickson and Arbour (2012)	• Population-based, retrospective cohort study using the British Columbia Perinatal Registry • Singleton pregnancies • n = 233,891 • 2001–2006 • British Columbia, Canada	• Nonsmokers: Never smoked • Quit smoking: Not further defined, timing not specified • Continued smoking: Smoking at first prenatal visit, subgrouped by smoking intensity: – Light: 1–4 cigarettes/day – Moderate: 5–9 cigarettes/day – Heavy: ≥10 cigarettes/day • Smoking history based on self-reports typically ascertained at the first prenatal visit (12–18 weeks' gestation)	Birth weight <3rd and <10th percentiles for gestational age	**Adjusted OR for SGA (95% CI):** • 3rd percentile: – Nonsmokers (reference) – Quit smoking: 0.86 (0.72–1.03) – Continued smoking: ○ Light: 1.33 (1.11–1.60) ○ Moderate: 1.82 (1.51–2.20) ○ Heavy: 2.37 (2.06–2.72) • 10th percentile: – Nonsmokers (reference) – Quit smoking: 0.84 (0.76–0.92) – Continued smoking: ○ Light: 1.24 (1.12–2.72) ○ Moderate: 1.74 (1.57–1.93) ○ Heavy: 2.14 (1.98–2.32)	Results adjusted for maternal age, parity, prenatal care visits, diabetes, hypertension, pre-pregnancy weight, presence of a partner, alcohol and drug use, and sex of the infant
Miyake et al. (2013)	• Retrospective cohort study • n = 1,565 • 2007–2008 • Japan	• Nonsmoker: Did not smoke during pregnancy • Quit smoking, first trimester: Smoked only during first trimester • Quit smoking, second or third trimester: Smoked during the second or third trimester but not throughout pregnancy • Continued smoking: Smoked throughout pregnancy • Smoking status for each trimester of pregnancy based on self-reports obtained after delivery	Birth weight <10th percentile for gestational age	**Adjusted OR for SGA (95% CI):** • Nonsmoker (reference) • Quit smoking, first trimester: – Overall: 0.53 (0.13–1.49) – Male infants: 1.02 (0.16–3.81) – Female infants: 0.24 (0.01–1.22) • Quit smoking, second or third trimester: – Overall: 1.93 (0.55–5.27) – Male infants: 1.67 (0.08–11.08) – Female infants: 2.14 (0.48–6.92) • Continued smoking: – Overall: 2.87 (1.11–6.56) – Male infants: 4.21 (1.26–12.14) – Female infants: 1.51 (0.23–5.96)	Results adjusted for region of residence; number of children; family structure; maternal age, education, employment, alcohol consumption, and BMI; gestational age at birth; and sex of the infant Did not account for substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Murphy et al. (2013)	• Prospective cohort study • Singleton pregnancies • n = 1,216 • 2010–2011 • Ireland	• Nonsmoker: Not defined • Quit smoking: Smoked during 6 months before pregnancy but quit by first prenatal visit • Continued smoking: Smoked during 6 months before pregnancy, at first • prenatal visit, and during third trimester • Smoking status based on self-reports obtained at enrollment and in third trimester	Birth weight <10th percentile, corrected for maternal height and weight, parity, infant sex, ethnicity, and gestation	**OR for SGA (95% CI):** • Nonsmoker (reference) • Quit smoking: – Unadjusted: 0.81 (0.46–1.40) – Adjusted: 1.05 (0.58–1.89) • Continued smoking: – Unadjusted: 2.09 (1.27–3.44), – Adjusted: 1.39 (1.06–1.84)	Birth weight adjusted for maternal age, nationality, unplanned pregnancy, private healthcare, alcohol use, and illicit drug use
Rode et al. (2013)	• Prospective cohort study • Singleton, term pregnancies • n = 1,774 • 1996–1999 • Denmark	• Nonsmokers: Not defined • Quit smoking: Quit immediately before or during pregnancy • Continued smoking: Not defined. • Smoking status based on self-reports assessed at 12–18 weeks' and 37 weeks' gestation and 1 year postpartum • Salivary cotinine obtained in a subgroup at 16 and 37 weeks' gestation	Birth weight <10th percentile for gestational age	**OR for SGA (95% CI):** • Nonsmokers (reference) • Quit smoking: – Unadjusted: 1.1 (0.7–1.7) – Adjusted: 1.0 (0.6–1.6) • Continued smoking: – Unadjusted: 3.5 (2.4–4.9) – Adjusted: 3.6 (2.5–5.2)	Birth weight adjusted for pre-pregnancy BMI, preeclampsia, and parity Salivary cotinine for subgroup reported but not integrated into main analysis Did not account for alcohol or substance use
Meghea et al. (2014)	• Prospective cohort study • n = 474 • 2008–2009 • Romania	• Nonsmokers: Not smoking when learned they were pregnant • Quit smoking: Quit upon learning of pregnancy • Continued smoking: Smoking at time of study interview (gestational age not reported) • Smoking history based on self-reports obtained at study enrollment (gestational age not reported)	Birth weight <10th percentile for gestational age	**Adjusted OR for SGA (95% CI):** • Nonsmokers (reference) • Quit smoking: 2.16 (1.05–4.43) • Continued smoking: 1.79 (0.74–4.32)	Results adjusted for stress, depressive symptoms, maternal age >35 years old, education, rural residence, marital status, and nulliparity Did not account for alcohol or substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Räisänen et al. (2014)	• Population-based study based on Finnish Medical Birth Register • Singleton pregnancies, live or stillborn after 22 weeks' gestation • n = 1,164,953 • 1991–2010 • Finland	• Nonsmokers: Not further defined • Quit smoking: Quit smoking during first trimester • Continued smoking: Smoked after first trimester • Smoking history ascertained from the Finnish Medical Birth Register	Birth weight >2 SD below sex- and parity-specific means for gestational age	**OR for SGA (95% CI):** • Nonsmokers (reference) • Quit smoking: – Unadjusted 1.33 (1.26–1.41) – Adjusted: 1.16 (1.09–1.23) • Continued smoking: – Unadjusted: 2.38 (2.33–2.44) – Adjusted: 2.47 (2.41–2.53)	Results adjusted for maternal age, parity, socioeconomic status, and sex of the infant Did not account for alcohol or substance use
Suzuki et al. (2014)	• Prospective cohort study • Singleton pregnancies • n = 2,663 • 1991–2006 • Japan	• moker: Never smoked • Quit smoking before pregnancy: Not further defined • Quit smoking, first trimester • Continued smoking: Smoked after first trimester • Smoking history based on self-reports obtained in early pregnancy (usually first trimester)	Birth weight <10th percentile using sex-specific growth curves for infants in Japan	**Adjusted OR for SGA (95% CI):** • Boys: – Nonsmokers (reference) – Quit smoking before pregnancy: 1.2 (0.5–3.2) – Quit smoking, first trimester: 1.0 (0.5–2.1) – Continued smoking: 3.2 (1.7–6.2) • Girls: – Nonsmokers (reference) – Quit smoking before pregnancy: 0.5 (0.1–1.5) – Quit smoking, first trimester: 1.1 (0.6–2.0) – Continued smoking: 2.5 (1.3–5.2)	Results adjusted for maternal age and BMI Did not account for alcohol or substance use
Blatt et al. (2015)	• Population-based retrospective cohort study using certificates of live births in Ohio • n = 927,424 • 2006–2012 • Ohio	• Nonsmoker: Did not smoke during 3 months before pregnancy or during pregnancy • Quit before pregnancy: Smoked during 3 months before pregnancy but not during pregnancy • Quit first trimester: Smoked only during first trimester • Quit second trimester: Smoked during first and second trimesters but not third trimester • Continued smoking: Smoked throughout pregnancy • Smoking history ascertained from vital statistics data and certificates of live births	Birthweight <10th and <5th percentiles for gestational age	**Adjusted OR for SGA (95% CI):** • <10th percentile: – Nonsmoker (reference) – Quit first trimester: 1.19 (1.13–1.24) – Quit second trimester: 1.67 (1.57–1.78) – Continued smoking: 2.26 (2.22–2.31) • <5th percentile: – Nonsmoker (reference) – Quit first trimester: 1.25 (1.17–1.33) – Quit second trimester: 1.83 (1.68–1.99) – Continued smoking: 2.44 (2.37–2.51)	Results adjusted for maternal age, race, education, marital status, hypertension, diabetes, and BMI Did not account for alcohol or substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Grzeskowiak et al. (2015)	• Retrospective cohort study • n = 7,658 • 2000–2005 • South Australia	• Nonsmokers • Quit smoking • Continued smoking • Smoking status not further defined • Smoking history based on self-reports ascertained at antenatal booking	Birth weight <10th percentile for gestational age by sex of the infant and maternal height and parity	**Percentage SGA:** • Nonsmokers: 7.1% (reference) • Quit smoking: 8.1%, p = 0.81 • Continued smoking: 15.3%, p <0.001	Results not adjusted for potential confounders Did not account for alcohol or substance use
Kvalvik et al. (2017)	• Population-based retrospective cohort study using the Medical Birth Registry of Norway • First and second births • n = 118,355 • 1999–2014 • Norway	• Nonsmoker: Did not smoke at the end of either pregnancy • Daily smoker/quit smoking: Smoked daily at end of first pregnancy but not smoking at end of second pregnancy • Nonsmoker/daily smoker: Not smoking at end of first pregnancy but smoked daily at end of second pregnancy • Daily smoker/daily smoker: Smoked daily at end of both pregnancies • Did not describe how smoking status was ascertained	Birth weight <10th and <2.5th percentile for gestational age by sex	**RR for SGA at second pregnancy (95% CI):** • <10th percentile: – Nonsmoker (reference) – Daily smoker/quit smoking: ○ Unadjusted: 1.5 (1.3–1.6) ○ Adjusted: 1.5 (1.3–1.7) – Nonsmoker/daily smoker: ○ Unadjusted: 2.1 (1.8–2.5) ○ Adjusted: 2.1 (1.8–2.5) – Daily smoker/daily smoker: ○ Unadjusted: 2.9 (2.7–3.1) ○ Adjusted: 2.9 (2.7–3.1) • < 2.5th percentile: – Nonsmoker (reference) – Daily smoker/quit smoking: ○ Unadjusted: 1.5 (1.1–2.0) ○ Adjusted: 1.5 (1.1–2.0) – Nonsmoker/daily smoker: ○ Unadjusted: 3.2 (2.4–4.3) ○ Adjusted: 3.1 (2.3–4.2) – Daily smoker/daily smoker: ○ Unadjusted: 4.0 (3.4–4.7) ○ Adjusted: 3.9 (3.3–4.6)	Results adjusted for maternal age, marital status, and year of first birth Did not account for alcohol or substance use

Table 4.33 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Tong et al. (2017)	• Population-based retrospective cohort study • n = 88,933 • 2009–2011 • United States	• Nonsmoker: Did not smoke during • 3 months before pregnancy or during last 3 months of pregnancy • Quit smoking: Smoked during 3 months before pregnancy but not during last • 3 months of pregnancy • Continued smoking, nondaily: Smoked during 3 months before pregnancy and • <1 cigarette/day during last 3 months of pregnancy • Continued smoking, daily: Smoked during 3 months before pregnancy and smoked ≥1 cigarette/day during last 3 months of pregnancy • Smoking status based on survey administered postpartum	≤10th percentile birth weight for gestational age by sex and race	**Prevalence ratio for SGA (95% CI):** • Nonsmoker (reference) • Quit smoking: – Unadjusted: 1.0 (0.9–1.1) – Adjusted: 0.9 (0.9–1.0) • Continued smoking: – Nondaily: ○ Unadjusted: 1.6 (1.3–1.9) ○ Adjusted: 1.4 (1.1–1.8) – Daily: ○ Unadjusted: 2.2 (2.0–2.4) ○ Adjusted: 2.0 (1.9–2.2)	Results adjusted for maternal age, parity, education, marital status, BMI, trimester of entry into prenatal care, and alcohol use during pregnancy Did not account for substance use

Notes: **BMI =** body mass index; **CI =** confidence interval; **OR =** odds ratio; **RR =** risk ratio; **SD =** standard deviation; **SGA =** small for gestational age.

(Mitchell et al. 2002; England et al. 2007; Pipkin 2008; Andersen et al. 2009; McCowan et al. 2009; Polakowski et al. 2009; Vardavas et al. 2010; Bakker et al. 2011; Baba et al. 2012; Erickson and Arbour 2012; Miyake et al. 2013; Murphy et al. 2013; Rode et al. 2013; Meghea et al. 2014; Räisänen et al. 2014; Suzuki et al. 2014; Blatt et al. 2015; Grzeskowiak et al. 2015; Tong et al. 2017), and 1 study compared them with the infants of continuing smokers (Bickerstaff et al. 2012). In general, these 20 studies found that women who continued to smoke past early pregnancy had an elevated risk of SGA delivery and that cessation attenuated or eliminated this excess risk.

Seven of the 20 studies examined a combined-exposure variable of cessation before pregnancy with cessation during early pregnancy, and thus could not isolate the effects of cessation by timeframe (before and after conception) (England et al. 2007; Andersen et al. 2009; Vardavas et al. 2010; Bickerstaff et al. 2012; Murphy et al. 2013; Rode et al. 2013; Tong et al. 2017). Six of these seven studies found no difference in SGA risk in quitters compared with nonsmokers (England et al. 2007; Andersen et al. 2009; Vardavas et al. 2010; Murphy et al. 2013; Rode et al. 2013; Tong et al. 2017), while one (Bickerstaff et al. 2012) found a significant decrease in risk among quitters compared with continuing smokers (aOR = 0.43; 95% CI, 0.33–0.57). In 2 of the 20 studies, the timing of cessation with respect to conception was not described (Pipkin 2008; Erickson and Arbour 2012). Pipkin and colleagues (2008) did not perform any testing for statistical significance; and Erickson and Arbour (2012) found no increased risk of SGA among infants of quitters. Six of the 20 studies included assessment of smoking status in late pregnancy (typically in the third trimester) (Mitchell et al. 2002; Bakker et al. 2011; Baba et al. 2012; Rode et al. 2013; Blatt et al. 2015; Tong et al. 2017), thus reducing any potential contribution of unidentified relapse. Of these studies, five found no significant increase in risk of SGA infants among quitters whose status was verified in late pregnancy, and one (Baba et al. 2013) found an increased risk for late, but not early, quitters. One of the six studies assessed timing by trimester (Blatt et al. 2015) and found significant increases in risk in both early quitters (smoked in first trimester only) and later quitters (smoked in first and second trimesters only) (aOR = 1.19; 95% CI, 1.13–1.24, and 1.67; 95% CI, 1.57–1.78, respectively) when compared with nonsmokers. One study included biochemical validation of smoking cessation (Rode et al. 2013) and combined preconception and early-pregnancy quitters. The study found no increase for SGA risk in quitters when compared with nonsmokers.

Of the two studies that examined smoking cessation across consecutive pregnancies, one found no increased risk of SGA in babies of women who quit by the second pregnancy compared with women who did not smoke in either pregnancy (Okah et al. 2007), and the other found a significant increase for SGA in quitters compared with women who did not smoke during either pregnancy (Kvalvik et al. 2017). However, the basis for the different findings is not clear. Both studies were population based, used an SGA definition of less than 10th percentile, and relied on self-reported smoking status, and both adjusted for several potential confounders (for maternal age, race, and medical risk factors for SGA, and for maternal age, marital status, and year of first birth, respectively). The two studies were conducted in different countries (United States and Norway, respectively), however, and although Okah and colleagues (2007) categorized smoking status as positive or negative for each pregnancy, Kvalvick and colleagues (2017) specifically assessed smoking status at the end of each pregnancy.

Summary of the Evidence. Since the 2004 Surgeon General's report confirmed that smoking cessation eliminates much of the reduction in birth weight caused by maternal smoking (USDHHS 2004), numerous studies have assessed the relationships between smoking and smoking cessation and SGA, and most have adjusted for multiple confounders. The evidence is sufficient to infer that smoking cessation before or during early pregnancy reduces the risk of SGA birth compared with continued smoking. The evidence is suggestive but not sufficient to infer that the risk of an SGA birth in women who quit smoking before or during early pregnancy does not differ from that for nonsmokers. The evidence is inadequate to determine the gestational age before which smoking cessation should occur to eliminate the effects of smoking on risk of SGA.

Preterm Delivery

Delivery before 37 completed weeks' gestation is a leading cause of neonatal morbidity and mortality (March of Dimes et al. 2012; Menon 2012; Blencowe et al. 2013; Katz et al. 2013), and this problem affects approximately 15 million births per year globally (World Health Organization 2017) and nearly 10% of births in the United States (Martin et al. 2017). Preterm delivery can be medically indicated (about two-thirds of all preterm deliveries) or spontaneous (about one-third of preterm deliveries). Spontaneous preterm delivery encompasses preterm labor, premature rupture of membranes, and spontaneous fetal loss. Medically indicated preterm delivery can be the outcome of numerous maternal and fetal conditions, including maternal chronic diseases, such as hypertension or diabetes, and pregnancy complications, such as preeclampsia, GDM, or abnormal placentation (Purisch and Gyamfi-Bannerman 2017). Numerous risk factors for spontaneous preterm delivery have been identified, including prior spontaneous preterm delivery, intrauterine

infections, shortened cervix, multifetal pregnancy, fetal abnormalities, uterine anomalies, Black race, interpregnancy interval less than 18 months, low socioeconomic status, low gestational weight gain, poor nutrition status, and advanced maternal age (Conde-Agudelo et al. 2006; USDHHS 2010; Purisch and Gyamfi-Bannerman 2017).

The 1990 Surgeon General's report identified a reduced risk of preterm delivery among women who quit smoking before or during pregnancy relative to continuing smokers, but the report found insufficient evidence to draw conclusions about the effects of smoking cessation on both preterm delivery and gestational duration (USDHHS 1990). The 2004 Surgeon General's report found a causal relationship between maternal smoking and preterm delivery (gestational age <37 weeks) and shorter gestational duration (number of days or weeks of pregnancy) (USDHHS 2004). The 2010 Surgeon General's report reviewed mechanisms hypothesized to explain the increased risk of preterm delivery among smokers, including increased risk of genitourinary tract infections, alterations in vaginal flora and localized immunosuppression, alterations in cervical cytokine profiles, reductions in maternal zinc levels, dysregulation of the fetal immune system, and alterations in myometrial contractility (USDHHS 2010).

Twenty-five studies published in 2000 or later that examined smoking cessation and preterm delivery were identified (Table 4.34). Two studies (Abrevaya 2008; Mohsin and Jalaludin 2008) examined cessation across two consecutive pregnancies, and 23 examined cessation in single pregnancies (Hrubá and Kachlik 2000; Vogazianos et al. 2005; McCowan et al. 2009; Polakowski et al. 2009; Anderka et al. 2010; Vardavas et al. 2010; Bakker et al. 2011; Baba et al. 2012; Bickerstaff et al. 2012; Erickson and Arbour 2012; Batech et al. 2013; Miyake et al. 2013; Murphy et al. 2013; Meghea et al. 2014; Räisänen et al. 2014; Bailey 2015; Smith et al. 2015; Yan and Groothuis 2015; Dahlin et al. 2016; Moore et al. 2016; Suzuki et al. 2016; Tong et al. 2017; Wallace et al. 2017). All but three studies (Hrubá and Kachlik 2000; Vogazianos et al. 2005; Suzuki et al. 2016) adjusted for at least some potential confounders, and five addressed alcohol consumption (McCowan et al. 2009; Bakker et al. 2011; Miyake et al. 2013; Yan and Groothuis 2015; Tong et al. 2017), while three addressed both alcohol and substance use (Erickson and Arbour 2012; Bailey 2015; Smith et al. 2015).

Of the 23 studies examining individual pregnancies, 8 classified exposure combining cessation before pregnancy with cessation during early pregnancy and, thus, could not estimate the effect of cessation after conception (Hrubá and Kachlik 2000; Anderka et al. 2010; Vardavas et al. 2010; Baba et al. 2012; Bickerstaff et al. 2012; Murphy et al. 2013; Dahlin et al. 2016; Tong et al. 2017). Of these eight studies, five compared quitters with nonsmokers and found no statistically significant difference in risk between the two groups (Vardavas et al. 2010; Baba et al. 2012; Murphy et al. 2013; Dahlin et al. 2016; Tong et al. 2017). Bickerstaff and colleagues (2012) compared quitters with continuing smokers and found no difference in risk. Six of the 23 studies examined cessation before conception; 4 compared quitters with nonsmokers (Vogazianos et al. 2005; Smith et al. 2015; Yan and Groothuis 2015; Moore et al. 2016). Three of the four found no significant differences in preterm deliveries (Vogazianos et al. 2005; Smith et al. 2015; Yan and Groothuis 2015), and one found a slightly reduced risk in quitters (Moore et al. 2016). One study compared women who quit before pregnancy with continuing smokers and found a significantly reduced risk of preterm delivery (Batech et al. 2013); and one study reported percentages of preterm infants for nonsmokers and women who quit before pregnancy (5.0% and 5.8%, respectively), as well as for other cessation groups, but adjustment for confounding was not performed, and only an overall chi-square test result was reported (Suzuki et al. 2016).

Twelve of the 23 studies examined cessation during pregnancy (McCowan et al. 2009; Polakowski et al. 2009; Bakker et al. 2011; Miyake et al. 2013; Meghea et al. 2014; Räisänen et al. 2014; Bailey 2015; Smith et al. 2015; Yan and Groothuis 2015; Moore et al. 2016; Suzuki et al. 2016; Wallace et al. 2017); of those, 7 found no statistically significant increase in the risk of preterm delivery in quitters compared with nonsmokers (McCowan et al. 2009; Bakker et al. 2011; Miyake et al. 2013; Meghea et al. 2014; Räisänen et al. 2014; Smith et al. 2015; Yan and Groothuis 2015). Moore and colleagues (2016) and Wallace and colleagues (2017) used data from state certificates of live birth in Ohio, and both found an increased risk of preterm delivery in those who quit late in pregnancy, but not in those who quit early in the pregnancy compared with nonsmokers. Using a large sample of more than 900,000 births, Moore and colleagues (2016) found an increase in risk among second-trimester quitters (aOR = 1.70; 95% CI, 1.60–1.80) but not in earlier quitters (first trimester) compared with those who were nonsmokers. Wallace and colleagues (2017) found an increased risk in third-trimester quitters (aOR = 1.81; 95% CI, 1.48–2.21) but not in second- or first-trimester quitters compared with nonsmokers. One study found a significant difference across smoking categories overall, but women who quit during pregnancy were not compared directly with other groups (Suzuki et al. 2016). In another study using a large sample of 900,000 births, significant reductions in the risk of preterm delivery were found among first- and second-trimester quitters compared with continuing smokers (aOR = 0.69; 95% CI, 0.65–0.74 and aOR = 0.87; 95% CI, 0.79–0.96, respectively)

Table 4.34 Studies on smoking cessation and preterm delivery

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Hrubá and Kachlik (2000)	• Retrospective, clinic-based study • Term, singleton deliveries • n = 1,147 • Years of data collection not reported • Czech Republic	• Nonsmoker: Never smoked • Quit smoking: Smoked but quit before pregnancy or during first trimester • Continued smoking: Smoked throughout pregnancy either daily or occasionally • Smoking status based on self-reports from interviews conducted shortly after delivery • Findings stratified by exposure to environmental tobacco smoke	≤36 weeks' gestation	**Percentage preterm delivery:** • Continued smoking: 10.0% • No exposure to environmental tobacco smoke: – Nonsmoker: 6.5% – Quit smoking: 6.3% – Continued smoking: 10.0% • Exposure to environmental tobacco smoke: – Nonsmoker: 9.4% – Quit smoking: 4.8%	Results not adjusted for potential confounders No statistical testing reported Did not account for alcohol or substance use
Vogazianos et al. (2005)	• Population-based, retrospective cohort study • n = 59,014 • 1990–1996 • Cyprus	• Nonsmokers: Did not smoke before or during pregnancy • Quit smoking: Smoked before but not during pregnancy • Continued smoking: Smoked before and during pregnancy • Not clear how many women quit smoking during pregnancy and how they were categorized • Smoking status based on maternal self-reports obtained during physician interviews	<38 weeks' gestation	**OR for preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking: 1.02 (0.73–1.43) • Continued smoking: 2.58 (2.05–3.25)	Results not adjusted for potential confounders Did not account for alcohol or substance use
Abrevaya et al. (2008)	• Population-based, retrospective cohort study using linked certificates of live births in Michigan • First and second pregnancies in which women smoked during the first pregnancy • n = 14,731 • n = 8,044 • 1989–2004 • Michigan	• Quit smoking between pregnancies: Smoked during first pregnancy but not during second pregnancy • Continued smoking: Smoked during first and second pregnancies • Smoking status based on smoking history collected from certificates of live births, which used one question on tobacco use during pregnancy (yes/no)	<37 weeks' gestation	**Adjusted OR for preterm delivery (95% CI):** • Quit smoking between pregnancies (reference) • Continued smoking: – 18–24 years of age: 1.04 (0.89–1.22) – 25–30 years of age: 1.12 (0.89–1.40)	Results adjusted for maternal race, education, income, population, interpregnancy interval, and year of birth; trimester of first prenatal visit; number of prenatal visits; presence of father's name on birth certificate; and first-birth value of the outcome Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Mohsin and Jalaludin (2008)	• Population-based retrospective cohort study • Consecutive singleton births • n = 244,480 • 1994–2004 • Australia	• Nonsmoker: Did not smoke during either pregnancy • Quit smoking between pregnancies: • Smoked during first pregnancy but not during second pregnancy • Resumed smoking between pregnancies: • Smoked during second pregnancy but not during first pregnancy • Continued smoking: Smoked during first and second pregnancies • Smoking status based on self-reports	<37 weeks' gestation	**Adjusted OR for preterm delivery at second pregnancy (95% CI):** • Nonsmoker (reference) • Quit smoking between pregnancies: 1.41 (1.29–1.55) • Resumed smoking between pregnancies: 1.43 (1.37–1.60) • Continued smoking: 1.89 (1.8–1.99)	Results adjusted for interpregnancy interval and other factors not explicitly
McCowan et al. (2009)	• Prospective cohort study designed to develop screening tests for pregnancy complications • 2004–2007 • n = 2,504 • New Zealand • and Australia	• Nonsmokers (did not smoke during pregnancy) • Quit smoking: Smoked during pregnancy but quit before the study interview (~15 weeks' gestation) • Continued smoking: Smoking at time of study interview (~15 weeks' gestation) • Smoking status based on self-reports ascertained at 15 weeks' gestation	Spontaneous preterm labor or preterm, premature rupture of membranes resulting in a preterm delivery at <37 weeks' gestation	**Adjusted OR for spontaneous preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking: 1.03 (0.49–2.18) • Continued smoking: 3.21 (1.42–7.23)	Results adjusted for demographic factors (maternal age, ethnicity, marital status, employment status, and BMI) and clinical risk factors (bleeding during pregnancy; folic acid use; multivitamin use; alcohol use at 15 weeks' gestation; and scores for depression, stress, or anxiety) Did not account for substance use
Polakowski et al. (2009)	• Population-based retrospective cohort study • Singleton deliveries, ≥28 weeks' gestation • n = 915,441 • 2005 • United States (11 states)	• Nonsmoker: Smoked zero cigarettes in all trimesters of pregnancy • Quit first trimester: Smoked during first trimester but not during second and third trimesters • Quit second trimester: Smoked during second trimester but not during third trimester • Continued smoking: Smoked during all three trimesters • Excluded women who did not fit in any of these categories • Smoking status based on certificates of live births	Preterm delivery 28–≤37 weeks' gestation based on last menstrual period, unless implausible (then based on clinical estimate)	**Adjusted OR for preterm delivery (95% CI):** • Preterm, non-SGA: – Continued smoking (reference) – Nonsmokers: 0.72 (0.70–0.74) – Quit first trimester: 0.69 (0.65–0.74) – Quit second trimester 0.87 (0.79–0.96) • Preterm, SGA: – Continued smoking (reference) – Nonsmokers: 0.45 (0.42–0.47) – Quit first trimester: 0.47 (0.40–0.55) – Quit second trimester: 0.88 (0.72–1.08)	Results adjusted for maternal age, race/ethnicity, marital status, education, late entry into prenatal care, and history of preterm delivery Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Anderka et al. (2010)	• Population-based, case-control study • n = 4,667 • 1997–2003 • United States	• Nonsmoker: Did not smoke during • 3 months before conception or during any trimester of pregnancy • Quit smoking: Smoked preconception but not during any trimester of pregnancy, smoked in first trimester but not in second or third trimesters, or smoked in second trimester but not in third trimester • Continued smoking: Smoked during all three trimesters • Smoking status based on maternal • self-reports obtained during interviews conducted 6 weeks–24 months postpartum	<37 weeks' gestation	**Percentage and adjusted OR for preterm delivery (95% CI):** • Nonsmoker 7.6% (reference) • Quit smoking: 8.0%, adjusted OR not reported • Continued smoking: 11.5%, 1.59 (1.13–2.25)	Results adjusted for maternal age, race/ethnicity, education, and birthplace Did not account for alcohol or substance use
Vardavas et al. (2010)	• Population-based, prospective cohort study • Singleton pregnancies • 2007–2008 • n = 1,400 • Greece	• Nonsmokers: Did not smoke during 3 months before pregnancy • Quit smoking: Smoked within 3 months before pregnancy and/or during the first 12 weeks of pregnancy but (quit by the time of study interview ~12 weeks' gestation) • Continued smoking: Smoked during 3 months before pregnancy, during first 12 weeks of pregnancy, and • at the time of the study interview (~12 weeks' gestation) • Smoking status based on self-reports ascertained at approximately 12 weeks' gestation	<37 weeks' gestation	**OR for preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking: – Unadjusted: 0.86 (0.54–1.38) – Adjusted: 0.90 (0.56–1.46) • Continued smoking: – Unadjusted: 1.22 (0.82–1.83) – Adjusted: 1.28 (0.84–1.94)	Results adjusted for origin, parity, maternal education and age, and sex of the infant Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Bakker et al. (2011)	• Population-based cohort study • 2001–2005 • n = 5,389 • Netherlands	• Nonsmokers: Did not smoke during pregnancy • Quit smoking, first trimester: Smoked only during first trimester (combined with "quit smoking, second and third trimesters" for analysis) • Quit smoking, second trimester: Smoked during second trimester (combined with "quit smoking, first and third trimesters" for analysis) • Continued smoking: Smoked during third trimester (combined with "quit smoking, first and second trimesters" for analysis) • Smoking status based on self-reports obtained during each trimester	<37 weeks' gestation	**Adjusted OR for preterm delivery (95% CI):** • Nonsmoker (reference) • Quit smoking, first trimester: 0.66 (0.37–1.17) • Continued smoking: 1.25 (0.88–1.78)	Results adjusted for maternal age, BMI, height, education, ethnicity, parity, alcohol consumption, caffeine intake, folic acid intake, and stress; gestational age at birth; and sex of the fetus Did not account for substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Baba et al. (2012)	• Population-based retrospective cohort study using the Swedish Medical Birth Register • n = 776,836 • 1999–2009 • Sweden	• Nonsmoker: Did not smoke during 3 months before pregnancy or before registration for antenatal care • Quit smoking: Smoked during 3 months before pregnancy but quit by registration for antenatal care • Continued smoking: Smoking at registration for antenatal care • Smoking status based on self-reports assessed at first antenatal visit (typically ≤15 weeks' gestation)	• Overall preterm delivery: <37 weeks' gestation • Very preterm delivery: <32 weeks' gestation • Moderate preterm delivery: 32–36 weeks' gestation • Spontaneous preterm delivery: Spontaneous onset of labor and preterm premature rupture • Induced preterm delivery: Vaginally induced onset of labor and cesarean delivery before the onset of labor	**OR for preterm delivery (95% CI):** • Nonsmoker (reference) • Quit smoking: – Unadjusted: ○ <37 weeks: 1.02 (0.99–1.06) ○ <32 weeks: 1.04 (0.94–1.15) ○ 32–36 weeks: 1.02 (0.98–1.06) – Adjusted: ○ <37 weeks: 0.90 (0.87–0.94) ○ <32 weeks: 0.91 (0.82–1.01) ○ 32–36 weeks: 0.90 (0.86–0.94) – Spontaneous preterm delivery: 0.92 (0.88–0.96) – Induced preterm delivery: 0.86 (0.79–0.92) • Continued smoking: – Unadjusted: ○ <37 weeks: 1.43 (1.38–1.48) ○ <32 weeks: 1.84 (1.69–2.00) ○ 32–36 weeks: 1.37 (1.32–1.41) – Adjusted: ○ <37 weeks: 1.30 (1.25–1.36) ○ <32 weeks: 1.68 (1.52–1.84) ○ 32–36 weeks: 1.25 (1.20–1.30) – Spontaneous preterm delivery: 1.32 (1.26–1.38) – Induced preterm delivery: 1.20 (1.12–1.29)	Results adjusted for BMI in early pregnancy, maternal age, parity, education, and cohabitation Did not account for alcohol or substance use
Bickerstaff et al. (2012)	• Retrospective cohort study • 1997–2006 • n = 30,524 • Australia	• Nonsmoker: Never smoked or quit • >12 months before booking • Quit smoking: Smoked during 12 months before booking but quit before booking • Continued smoking: Currently smoking at booking • Smoking status based on routinely collected clinical data	<37 weeks' gestation	**Percentage with preterm delivery:** • Nonsmoker: 9.7% • Quit smoking: 12.7% • Continued smoking: 12.9% **Adjusted OR for preterm delivery (95% CI):** • Continued smoking vs. nonsmoker: 1.42 (1.28–1.59) • Quit smoking vs. continued smoking: 0.92 (0.69–1.23)	Results adjusted for plurality, previous pregnancy complications, parity, and ethnicity Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Yan and Groothuis (2015)	• Population-based cohort study • Singleton pregnancies • Excluded women with chronic diseases • n = 11,131 • 2000–2001 • United Kingdom	• Nonsmokers: Not defined • Quit smoking before pregnancy: Timing of cessation not specified • Quit smoking during pregnancy (month of cessation noted) • Continued smoking: Quit during third trimester or did not quit • Smoking history based on self-reports ascertained when infants were 9 months old	<37 weeks' gestation, based on gestational age estimated by research team	**Difference in percentage of preterm delivery:** • Nonsmokers (reference) • Quit smoking before pregnancy: +0.8% • Quit smoking, first trimester: +0.1%, p = 0.8 • Quit smoking, second trimester: 2.8%, p = 0.08 • Continued smoking: +2.9%, p <0.01	Adjusted for birth year/quarter of infant and maternal weight, height, income, initiation of prenatal care, alcohol use, employment status, home satisfaction, religion affiliation, and racist or religion-based insults in living area Did not account for substance use
Dahlin et al. (2016)	• Population-based, retrospective cohort study using the Swedish Medical Birth Register • n = 1,371,274 • 1999–2012 • Sweden	• Nonsmokers: No antenatal tobacco use • Quit smoking: Smoked during 3 months before pregnancy but quit by the first antenatal visit • Continued smoking: Smoked ≥1 cigarette/day at the time of the first antenatal visit • Smoking status based on self-reports derived from the Swedish Medical Birth Register	• Extreme preterm delivery: <28 weeks' gestation • Very preterm delivery: 28–31 weeks' gestation • Moderate preterm delivery: 32–36 weeks' gestation	**OR for preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking: – Unadjusted preterm delivery: ○ Extreme: 1.12 (0.97–1.29) ○ Very: 1.03 (0.93–1.13) ○ Moderate: 1.05 (1.02–1.08) – Adjusted preterm delivery: ○ Extreme: 1.02 (0.88–1.18) ○ Very: 0.92 (0.83–1.02) ○ Moderate: 0.94 (0.91–1.01) • Continued smoking: – Unadjusted preterm delivery: ○ Extreme: 1.87 (1.64–2.12) ○ Very: 1.68 (1.54–1.83) ○ Moderate: 1.39 (1.34–1.43) – Adjusted preterm delivery: ○ Extreme: 1.74 (1.51–1.99) ○ Very: 1.52 (1.38–1.67) ○ Moderate: 1.27 (1.23–1.31)	Results adjusted for maternal age, parity, cohabitation with father, country of birth, education, and BMI Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Murphy et al. (2013)	• Prospective cohort study • Singleton pregnancies • n = 1,216 • 2010–2011 • Dublin, Ireland	• Nonsmoker: Not defined • Quit smoking: Smoked during 6 months before pregnancy but quit by first prenatal visit • Continued smoking: Smoked during 6 months before pregnancy, and smoking at first prenatal visit and during third trimester • Smoking status based on self-reports obtained at enrollment and during third trimester	<37 weeks' gestation	**Crude and adjusted OR for preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking: – Crude: 1.14 (0.51–2.56) – Adjusted: 1.68 (0.51–5.63) • Continued smoking: – Crude: 1.25 (0.51–3.10) – Adjusted: 1.09 (0.86–1.75)	Birth weight adjusted for maternal age, BMI, nationality, unplanned pregnancy, private healthcare, alcohol use, and illicit drug use
Meghea et al. (2014)	• Prospective cohort study • n = 474 • 2008–2009 • Romania	• Nonsmokers: Not smoking when learned of pregnancy • Quit smoking: Quit upon learning of pregnancy • Continued smoking: Smoking at time of study interview (gestational age not reported) • Smoking history based on self-reports obtained at study enrollment (gestational age not reported)	<37 weeks' gestation	**Odds ratio for preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking: 1.41 (0.59–3.37) • Continued smoking: 1.29 (0.46–3.67)	Results adjusted for stress, depressive symptoms, maternal age >35 years old, education, rural residence, marital status, and nulliparity Did not account for alcohol or substance use
Räisänen et al. (2014)	• Population-based retrospective cohort using Finnish Medical Birth Register • Singleton deliveries, live or stillborn after 22 weeks' gestation • n = 1,164,953 • 1991–2010 • Finland	• Nonsmokers: Not further defined • Quit smoking: Quit smoking during first trimester • Continued smoking: Smoked after first trimester • Smoking history based on self-reports ascertained from the Finnish Medical Birth Register	<37 weeks' gestation	**Adjusted OR (95% CI):** • Nonsmokers (reference) • Quit smoking: – Unadjusted: 1.04 (0.98–1.10) – Adjusted: 1.01 (0.95–1.07) • Continuing smokers: – Unadjusted: 1.35 (1.31–1.38) – Adjusted: 1.39 (1.36–1.43)	Results adjusted for maternal age, parity, socioeconomic status, and sex of the infant Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Bailey (2015)	• Randomized clinical trial of smoking cessation intervention • 2008–2012 • n = 1,486 • Tennessee	• Quit smoking: Smoked at first prenatal visit but quit by third trimester • Continued smoking: Smoked at first prenatal visit and still smoking during third trimester • Smoking history based on self-reports obtained at first prenatal visit • Quit status ascertained during third trimester by exhaled CO and urine cotinine and by self-report at delivery	Preterm delivery not defined	**Percentage preterm delivery (95% CI):** • Quit smoking: 9.8% • Continued smoking: 13.8% • p = 0.089	Randomized cessation trial and thus no comparison group of never smokers Results adjusted for maternal age, education, marital status, insurance status, and marijuana use Examined maternal race, previous pregnancies, live deliveries, and alcohol use, but they were not significant in the model
Smith et al. (2015)	• Population-based case-cohort study • n = 1,887 • 2009–2010 • United Kingdom	• Nonsmoker: Did not smoke during preconception or early (1–13 weeks) or late (14–32 weeks) during pregnancy • Quit smoking before pregnancy: Smoked preconception but not during early or late pregnancy • Quit smoking, first trimester: Smoked during early pregnancy but not during late pregnancy • Continued smoking: Smoked during late pregnancy • Smoking status based on self-reports obtained from maternal interview conducted shortly after delivery	32–36 weeks' gestation	**Adjusted RR for preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking before pregnancy: 0.93 (0.72–1.20) • Quit smoking, first trimester: 1.12 (0.76–1.66) • Continued smoking: 1.38 (1.04–1.84)	Results adjusted for maternal age, ethnicity, BMI, education level, and lifestyle factors (recreational drug and alcohol use, dietary practices, and folic acid supplements)

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Yan and Groothuis (2015)	• Population-based cohort study • Singleton pregnancies • Excluded women with chronic diseases • n = 11,131 • 2000–2001 • United Kingdom	• Nonsmokers: Not defined • Quit smoking before pregnancy: Timing of cessation not specified • Quit smoking during pregnancy (month of cessation noted) • Continued smoking: Quit during third trimester or did not quit • Smoking history based on self-reports ascertained when infants were 9 months old	<37 weeks' gestation, based on gestational age estimated by research team	**Difference in percentage of preterm delivery:** • Nonsmokers (reference) • Quit smoking before pregnancy: +0.8% • Quit smoking, first trimester: +0.1%, p = 0.8 • Quit smoking, second trimester: 2.8%, p = 0.08 • Continued smoking: +2.9%, p <0.01	Adjusted for birth year/quarter of infant and maternal weight, height, income, initiation of prenatal care, alcohol use, employment status, home satisfaction, religion affiliation, and racist or religion-based insults in living area Did not account for substance use
Dahlin et al. (2016)	• Population-based, retrospective cohort study using the Swedish Medical Birth Register • n = 1,371,274 • 1999–2012 • Sweden	• Nonsmokers: No antenatal tobacco use • Quit smoking: Smoked during 3 months before pregnancy but quit by the first antenatal visit • Continued smoking: Smoked ≥1 cigarette/day at the time of the first antenatal visit • Smoking status based on self-reports derived from the Swedish Medical Birth Register	• Extreme preterm delivery: <28 weeks' gestation • Very preterm delivery: 28–31 weeks' gestation • Moderate preterm delivery: 32–36 weeks' gestation	**OR for preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking: – Unadjusted preterm delivery: ○ Extreme: 1.12 (0.97–1.29) ○ Very: 1.03 (0.93–1.13) ○ Moderate: 1.05 (1.02–1.08) – Adjusted preterm delivery: ○ Extreme: 1.02 (0.88–1.18) ○ Very: 0.92 (0.83–1.02) ○ Moderate: 0.94 (0.91–1.01) • Continued smoking: – Unadjusted preterm delivery: ○ Extreme: 1.87 (1.64–2.12) ○ Very: 1.68 (1.54–1.83) ○ Moderate: 1.39 (1.34–1.43) – Adjusted preterm delivery: ○ Extreme: 1.74 (1.51–1.99) ○ Very: 1.52 (1.38–1.67) ○ Moderate: 1.27 (1.23–1.31)	Results adjusted for maternal age, parity, cohabitation with father, country of birth, education, and BMI Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Moore et al. (2016) (continues on next page)	• Population-based, retrospective cohort using certificates of live births in Ohio • Singleton births without congenital anomalies • n = 913,757 • 2006–2012 • Ohio	• Nonsmoker: Did not smoke during 3 months before pregnancy • Quit smoking before pregnancy: Smoked during 3 months before pregnancy but not during first trimester • Quit smoking, first trimester: Smoked during first trimester but not during second and third trimesters • Quit smoking, second trimester: Smoked during second trimester but not during third trimester • Continued smoking: Smoked during all three trimesters • Smoking status obtained from Ohio certificates of live birth	• Overall preterm delivery: <37 weeks' gestation based on clinician's best estimate of gestational age • Extreme preterm delivery: 20–27 weeks' gestation • Preterm delivery: 28–36 weeks' gestation • Spontaneous preterm delivery: Not medically indicated • Indicated preterm delivery: Births complicated by intrauterine growth restriction, preeclampsia, or eclampsia following induction of labor	**Adjusted OR for preterm delivery (95% CI):** • Overall: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.91 (0.88–0.94) – Quit smoking, first trimester: 1.02 (0.98–1.07) – Quit smoking, second trimester: 1.70 (1.60–1.80) – Continued smoking: 1.21 (1.19–1.24) • Extreme preterm: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.87 (0.77–0.98) – Quit smoking, first trimester: 1.20 (1.03–1.40) – Quit smoking, second trimester: Not applicable – Continued smoking: 0.90 (0.83–0.97) • Preterm: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.91 (0.88–0.94) – Quit smoking, first trimester: 1.01 (0.96–1.05) – Quit smoking, second trimester: 1.46 (1.37–1.55) – Continued smoking: 1.24 (1.21–1.26)	Results adjusted for maternal race, education, age, Medicaid, marital status, and parity

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
(continued from previous page) Moore et al. (2016) (continues on next page)	—	—	—	**Indicated preterm delivery (95% CI):** • Overall: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.92 (0.87–0.97) – Quit smoking, first trimester: 1.01 (0.94–1.09) – Quit smoking, second trimester: 1.78 (1.62–1.96) – Continued smoking: 1.22 (1.18–1.26) • Extreme preterm: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.85 (0.78–0.93) – Quit smoking, first trimester: 0.93 (0.82–1.05) – Quit smoking, second trimester: Not applicable – Continued smoking: 0.73 (0.69–0.78) • Preterm: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.91 (0.87–0.96) – Quit smoking, first trimester: 0.99 (0.92–1.07) – Quit smoking, second trimester: 1.66 (1.51–1.83) – Continued smoking: 1.18 (1.14–1.22)	—

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
(continued from previous page) Moore et al. (2016)	—	—	—	**Spontaneous preterm delivery (95% CI):** • Overall: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.90 (0.87–0.93) – Quit smoking, first trimester: 1.03 (0.97–1.08) – Quit smoking, second trimester: 1.65 (1.54–1.77) – Continued smoking: 1.20 (1.17–1.22) • Extreme preterm: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.88 (0.77–1.02) – Quit smoking, first trimester: 1.20 (1.00–1.43) – Quit smoking, second trimester: Not applicable – Continued smoking: 0.93 (0.84–1.02) • Preterm: – Nonsmoker (reference) – Quit smoking before pregnancy: 0.90 (0.87–0.94) – Quit smoking, first trimester: 1.02 (0.96–1.08) – Quit smoking, second trimester: 1.37 (1.26–1.48) – Continued smoking: 1.25 (1.22–1.28)	—
Suzuki et al. (2016)	• Population-based, cohort study • Singleton pregnancies • n = 7734 • 2011–2014 • Japan	• Nonsmokers: Never smoked • Quit smoking before pregnancy: Not further defined • Quit smoking during early pregnancy: Not further defined • Continued smoking: Currently smoking at time study questionnaire was administered • Smoking status based on self-reports collected during second trimester	Preterm delivery not defined	**Percentage preterm delivery:** • Nonsmoker: 5.0% • Quit smoking before pregnancy: 5.8% • Quit smoking during early pregnancy: 5.6% • Continued smoking: 8.9% • Chi-square test p = 0.008	Results not adjusted for potential confounders Did not account for alcohol or substance use

Table 4.34 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Wallace et al. (2017)	• Population-based, retrospective cohort study using certificates of live births in Ohio • Singleton pregnancies • Excluded congenital malformations • All participants had at least one previous preterm delivery • 2006–2012 • n = 36,432 • Ohio	• Nonsmoker: Did not smoke during 3 months before pregnancy • Quit smoking by first trimester: Smoked during 3 months before pregnancy but not during first trimester • Quit by second trimester: Smoked during first trimester but not during second or third trimesters • Quit by third trimester: Smoked during second trimester but not during third trimester • Continued smoking: Smoked during all three trimesters • Smoking status obtained from Ohio certificates of live birth	<37 weeks' gestation	**Adjusted OR for preterm delivery (95% CI):** • Nonsmokers (reference) • Quit smoking by first trimester: 0.97 (0.86–1.09) • Quit smoking by second trimester: 1.10 (0.93–1.29) • Quit smoking by third trimester: 1.81 (1.48–2.21) • Continued smoking: 1.14 (1.07–1.22)	Results adjusted for maternal race, marital status, and Medicaid enrollment Did not account for alcohol or substance use
Tong et al. (2017)	• Population-based, retrospective cohort study • n = 88,933 • 2009–2011 • United States	• Nonsmoker: Did not smoke during past 2 years and did not smoke during 3 months before pregnancy • Quit smoking: Smoked during 3 months before pregnancy but not during last 3 months of pregnancy • Continued smoking, nondaily: Smoked during 3 months before pregnancy and smoked <1 cigarette/day in last 3 months of pregnancy • Continued smoking, daily: Smoked during 3 months before pregnancy and smoked ≥1 cigarette/day during last 3 months of pregnancy	<37 weeks' gestation based on clinical estimate of gestation from birth certificates	**Crude and adjusted prevalence ratio for preterm delivery (95% CI):** • Nonsmoker (reference) • Quit smoking: – Crude: 1.0 (0.9–1.1) – Adjusted: 1.0 (0.9–1.1) – Continued smoking, nondaily: – Crude: 1.0 (0.8–1.3) – Adjusted: 1.0 (0.8–1.2) • Continued smoking, daily: – Crude 1.3: (1.2–1.4) – Adjusted: 1.3 (1.2–1.4)	Prevalence ratios adjusted for maternal age, parity, education, marital status, BMI, trimester of entry into prenatal care, and alcohol use during pregnancy Did not account for substance use

Notes: **BMI =** body mass index; **CI =** confidence interval; **CO =** carbon monoxide; **OR =** odds ratio; **RR =** risk ratio; **SGA =** small for gestational age.

(Polakowski et al. 2009), and in a smaller study, no significant difference was found between quitters and continuing smokers (Bailey 2015). Three studies were not sufficiently large to examine cessation during pregnancy, and the CIs were wide (McCowan et al. 2009; Miyake et al. 2013; Meghea et al. 2014).

In one of the 23 studies examining individual pregnancies, the timing of cessation was not described (Erickson and Arbour 2012); in that study, a modest but significant increase in risk was found among quitters compared with nonsmokers (aOR = 1.18; 95% CI, 1.08–1.28). Only 1 of the 23 studies included biochemical validation of smoking status (Bailey 2015); that study was a randomized clinical trial of a smoking cessation intervention (n = 1,486 who received the intervention vs. 461 who received usual care) in which no statistically significant difference was found in the risk of preterm delivery among women in the intervention group between women who quit smoking during pregnancy and continuing smokers (13.8% among continuing smokers and 9.8% among quitters [p = 0.09]).

Of the two studies that examined cessation across pregnancies, one found an increased risk of preterm delivery in the second pregnancy in women who quit between pregnancies versus those who did not smoke in either (aOR = 1.41; 95% CI, 1.29–1.55) (Mohsin and Jalaludin 2008), and the other found no difference in the risk of preterm delivery during the second pregnancy for women who quit between pregnancies compared with those who smoked during both pregnancies (Abrevaya 2008). As was previously discussed, examining outcomes across pregnancies can be limited by an oversimplification of exposure categories, but this design can reduce the contributions of confounding from environmental and genetic factors. If smoking cessation during pregnancy affects the risk of preterm delivery, then the effect could be missed using this method.

Summary of the Evidence. Since the 2004 Surgeon General's report found a causal relationship between maternal smoking and preterm delivery (gestational age <37 weeks) and shorter gestational duration (USDHHS 2004), numerous studies have assessed the relationships between smoking cessation before and/or during pregnancy and preterm delivery, and most have adjusted for multiple confounders. Most of these studies compared the risk of preterm delivery in quitters to that in nonsmokers, while fewer studies directly compared the risk in quitters to that in continuing smokers. The majority of studies that compared quitters and nonsmokers found no difference in risk of preterm delivery, and studies that compared quitters and continuing smokers reported mixed results (all reported lower risk in quitters compared with continuing smokers overall, but not all findings were significant). There were limited data with which to assess the role of timing of cessation for risk of preterm delivery, but the largest studies that examined trimester-specific cessation reported that earlier cessation produces greater benefits for risk of preterm delivery than later cessation. The evidence is suggestive but not sufficient to infer that the risk of preterm delivery in women who quit smoking before or during early pregnancy does not differ from that of nonsmokers. The evidence is suggestive but not sufficient to infer that women who quit smoking before conception or during early pregnancy have a reduced risk of preterm delivery compared with women who continue to smoke.

Stillbirth, Perinatal Mortality, and Infant Mortality

Stillbirth (typically defined as a fetal death after 28 weeks' gestation), perinatal mortality (stillbirths and deaths in the first week of life), and infant mortality (neonatal [death in the first month of life] and postnatal [death from 1 month to 1 year of life]) have all been associated with prenatal exposure to tobacco in previous Surgeon General's reports. The 1990 Surgeon General's report on smoking cessation presented evidence that women who quit smoking are at lower risk of perinatal mortality relative to continuing smokers, although the studies were too few to be conclusive (USDHHS 1990). No conclusions were drawn about the relationship between smoking cessation and infant mortality. The 2004 and 2014 Surgeon General's reports concluded that infants of smokers are at higher risk of stillbirth, perinatal mortality, and neonatal mortality than infants of nonsmokers (USDHHS 2004, 2014). Overall, these reports did not review the effects of cessation on these risks. The 2004 Surgeon General's report also found that smoking during or after pregnancy increases the risk of sudden infant death syndrome, but this outcome was not reviewed in this report due to the lack of studies directly assessing the consequences of smoking cessation on sudden infant death syndrome (USDHHS 2004).

Stillbirth, perinatal, and infant mortality are multifactorial in etiology, and many of their causal factors are also causally associated with smoking. For example, smoking is causally associated with preterm delivery, PPROM, placenta previa, and placental abruption—all of which contribute to perinatal and neonatal mortality; and preterm delivery accounts for more than one-third of infant deaths (Matthews et al. 2015). Therefore, the effects of cessation on those pathways would likely translate into beneficial effects on more distal outcomes. In addition, approximately half of perinatal deaths in the United States are stillbirths, and half are deaths in the first week

of life. Therefore, effects of smoking cessation on stillbirth or deaths in the first week of life likely also affect rates of perinatal mortality. The relationship between smoking and fetal growth was explored in depth in the 2014 Surgeon General's report (USDHHS 2014). Briefly, when the distributions of birth weight for the infants of smokers and their corresponding mortality rates are examined, infants of smokers have higher mortality than those of nonsmokers at every birth weight when each population is adjusted to its own z-scale for birth weight (Wilcox 2001). Thus, maternal smoking affects infant mortality independently of its effects on birth weight. Infants of nonsmokers are less likely to be born with low birth weight than those of smokers, but when they are, the underlying etiologies are associated with higher mortality (Wilcox 2001).

Stillbirth

Five studies published after 2000 were identified that examined smoking cessation and stillbirth; four examined cessation with respect to individual pregnancies (Wisborg et al. 2001; Erickson and Arbour 2012; Räisänen et al. 2014; Bjørnholt et al. 2016), and one examined cessation across two consecutive pregnancies (Högberg and Cnattingius 2007) (Table 4.35). All four studies examining cessation with respect to individual pregnancies included adjustment for at least some confounders, and two included adjustment for alcohol use or for alcohol and other substance use (Wisborg et al. 2001; Erickson and Arbour 2012). Three studies relied on data from registries (Erickson and Arbour 2012; Räisänen et al. 2014; Bjørnholt et al. 2016), and none included biochemical validation of cessation status. Two studies examined women who quit smoking during early pregnancy (Räisänen et al. 2014; Bjørnholt et al. 2016), and one (Wisborg et al. 2001) assessed smoking status in late pregnancy (30 weeks). No studies examined both the effects of quitting early versus quitting late in pregnancy. Three studies found no increased risk of stillbirth among women who quit smoking during early pregnancy compared with nonsmokers (Wisborg et al. 2001; Räisänen et al. 2014; Bjørnholt et al. 2016), and one found increased risk in quitters but not in continuing smokers (Erickson and Arbour 2012). This last study, however, did not address the timing of cessation in quitters with respect to pregnancy, and smoking status was ascertained only at the first prenatal visit, making it possible that some former smokers had relapsed by the end of pregnancy compared with women who smoked in neither pregnancy. However, the risk of stillbirth in the second pregnancy was significantly elevated among women who smoked during both pregnancies.

In the study that examined cessation across consecutive pregnancies (Högberg and Cnattingius 2007), a large, population-based study using data from the Swedish Medical Birth Register, women who smoked during the first pregnancy but not during the second pregnancy did not have an increased risk of stillbirth in the second pregnancy.

Summary of the Evidence

Since the 2004 and 2014 Surgeon General's reports found that infants of smokers are at higher risk of stillbirth than infants of nonsmokers (USDHHS 2004, 2014), several studies have examined the effects of smoking cessation on the risk of stillbirth, and findings have been mixed. These studies were limited by a lack of biochemical validation and inconsistent assessment of the timing of cessation during preconception and gestation. Consequently, the evidence is inadequate to infer that smoking cessation during pregnancy reduces the risk of stillbirth compared with continued smoking.

Perinatal Mortality

Two studies published after 2000 were identified that examined smoking cessation and perinatal mortality (Bickerstaff et al. 2012; Bailey 2015) (Table 4.36). Bickerstaff and colleagues (2012) examined risk in a retrospective cohort study of Australian women who had quit smoking in the year before pregnancy or after becoming pregnant but before the first antenatal visit, while Bailey (2015) examined risk in women participating in a randomized smoking cessation trial in the state of Tennessee who smoked during the first trimester of pregnancy but had quit by the third trimester. These two studies relied on self-reported tobacco use and adjusted for several potential confounders. Both studies found a reduction in the risk of perinatal mortality in quitters compared with continuing smokers, with findings from Bailey (2015) reaching statistical significance. Neither study compared quitters with nonsmokers.

Summary of the Evidence

Since the 2004 and 2014 Surgeon General's reports concluded that children of smokers are at higher risk of perinatal mortality than children of nonsmokers (USDHHS 2004, 2014), few studies have addressed smoking cessation and perinatal mortality. The evidence is inadequate to determine whether cessation before or during pregnancy reduces the risk of perinatal mortality compared with continued smoking.

Infant Mortality

Three studies published later than 2000 were identified that examined smoking cessation and infant death

Table 4.35 Studies on smoking cessation and stillbirth

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Wisborg et al. (2001)	• Prospective cohort study • Singleton pregnancies • n = 25,102 • 1989–1996 • Denmark	• Nonsmokers: Not smoking at time of either antenatal interview • Quit smoking: Stopped smoking by second antenatal interview • Continued smoking: Smoking ≥1 cigarette/day at both antenatal interviews • Smoking status ascertained from maternal interviews conducted before first antenatal visit (typically 16 weeks' gestation) and before the 30-week antenatal visit	Death of a fetus at or after 28 weeks' gestation	**Crude and adjusted OR for stillbirth (95% CI):** • Nonsmokers (reference) • Quit smoking: – Unadjusted: 0.9 (0.5–1.9) – Adjusted: 0.9 (0.5–1.9) • Continued smoking: – Unadjusted: 2.0 (1.4–2.9) – Adjusted: 1.9 (1.3–2.9)	Results adjusted for parity; maternal age, education, employment, caffeine and alcohol intake, weight, and height; and sex of the infant Did not account for substance use
Högberg and Cnattingius (2007)	• Population-based cohort study • First and second singleton births • n = 526,691 • 1983–2001 • Sweden	• Nonsmokers: Not smoking daily at time of first antenatal visit • Moderate smoker: Smoking 1–9 cigarettes/day at time of first antenatal visit • Heavy smoker: Smoking ≥10 cigarettes/day at time of first antenatal visit • Quit smoking: Not smoking in second pregnancy • Smoking history ascertained from medical birth registry, which included smoking status collected at first antenatal visit (typically <15 weeks' gestation)	Fetal death after at least 28 completed weeks' gestation	**Crude and adjusted OR for stillbirth in pregnancy (95% CI):** • Nonsmoker both pregnancies (reference) • Nonsmoker/moderate smoker: – Unadjusted: 0.85 (0.54–1.32) – Adjusted: 0.82 (0.52–1.30) • Nonsmoker/heavy smoker: – Unadjusted: 1.09 (0.49–2.45) – Adjusted: 0.92 (0.38–2.22) • Moderate smoker/nonsmoker (quit smoking): – Unadjusted: 1.17 (0.91–1.50) – Adjusted: 1.11 (0.85–1.44) • Moderate smoker/moderate smoker: – Unadjusted: 1.15 (0.92–1.43) – Adjusted: 1.16 (0.92–1.46) • Moderate smoker/heavy smoker: – Unadjusted: 1.64 (1.21–2.23) – Adjusted: 1.56 (1.13–2.16) • Heavy smoker/nonsmoker (quit smoking): – Unadjusted: 0.88 (0.51–1.51) – Adjusted: 0.67 (0.36–1.26) • Heavy smoker/moderate smoker: – Unadjusted: 1.50 (1.09–2.06) – Adjusted: 1.41 (1.01–1.96) • Heavy smoker/heavy smoker: – Unadjusted: 1.70 (1.32–2.19) – Adjusted: 1.55 (1.17–2.04)	Results adjusted for maternal age, education, cohabitation with the father, mother's country of birth, interpregnancy interval, stillbirth in first pregnancy, and year of second delivery Did not account for alcohol or substance use

Table 4.35 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Erickson and Arbour (2012)	• Population-based retrospective cohort study using the British Columbia Perinatal Database Registry • Singleton deliveries • n = 233,891 • 2001–2006 • British Columbia, Canada	• Nonsmoker: Never smoked • Quit smoking: Former smoker (time of cessation in former smokers with respect to pregnancy was not available) • Continued smoking: Current smoker at time of smoking status assessment • Light: 1–4 cigarettes/day • Moderate: 5–9 cigarettes/day • Heavy: ≥10 cigarettes/day • Smoking history based on self-reports typically ascertained at first prenatal visit	Fetal death ≥20 weeks' gestation or >500 g	**Adjusted OR for stillbirth (95% CI):** • Nonsmoker (reference) • Quit smoking: 1.43 (1.03–2.00) • Continued smoking – Light: 1.08 (0.67–1.72) – Moderate: 1.19 (0.71–1.97) – Heavy: 1.40 (0.97–2.03)	Results adjusted for parity; prenatal care visits; maternal age, diabetes, hypertension, pre-pregnancy weight, and alcohol and drug use; presence of a partner; and sex of the infant
Räisänen et al. (2014)	• Population-based retrospective cohort using Finnish Medical Birth Register • Singleton deliveries, live or stillborn after 22 weeks' gestation • 1991–2010 • n = 1,164,953 • Finland	• Nonsmokers: Not further defined • Quit smoking: Quit smoking during first trimester • Continued smoking: Smoked after first trimester • Smoking history based on self-reports ascertained from the Finnish Medical Birth Register • Details on when and how data were collected were not reported	Stillbirth definition not provided	**OR for stillbirth (95% CI):** • Reference (nonsmokers) • Quit smoking: – Unadjusted: 0.70 (0.60–0.81) – Adjusted: 1.07 (0.92–1.26) • Continued smoking: – Unadjusted: 1.03 (0.97–1.10) – Adjusted: 1.13 (1.06–1.20)	Results adjusted for maternal age, parity, socioeconomic status, and sex of the infant Did not account for alcohol or substance use
Bjørnholt et al. (2016)	• Population-based cohort study using the Danish Medical Birth Register • Singleton births • n = 841,228 • 1997–2010 • Denmark	• Nonsmoker: Did not smoke during pregnancy • Quit smoking: Quit during first trimester or early in second trimester • Continued smoking: Still smoking at time of first antenatal visit • Smoking status ascertained from maternal interviews at first antenatal visit (13–15 weeks' gestation)	• 1997–2004: Fetal death after 28 completed weeks' gestation • 2004–2010: Fetal death after 22 completed weeks' gestation • Stillbirth further categorized as antepartum (before delivery) or intrapartum (during delivery)	**Adjusted OR for stillbirth (95% CI):** • All: – Nonsmoker (reference) – Quit smoking: 1.03 (0.80–1.32) – Continued smoking: 1.47 (1.35–1.62) • Antepartum: – Nonsmoker (reference) – Quit smoking: 0.83 (0.61–1.13) – Continued smoking: 1.45 (1.31–1.61) • Intrapartum: – Nonsmoker (reference) – Quit smoking: 1.94 (1.10–3.41) – Continued smoking: 1.47 (1.12–1.92)	Results adjusted for year of delivery, maternal age, and marital or partner status

Notes: **CI =** confidence interval; **OR =** odds ratio.

Table 4.36 Studies on smoking cessation and perinatal mortality

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Bickerstaff et al. (2012)	• Retrospective cohort study • 1997–2006 • n = 30,524 • Australia	• Nonsmoker: Never smoked or quit >12 months before booking • Quit smoking: Smoked during 12 months before booking but quit before booking • Continued smoking: Currently smoking at booking • Smoking status based on routinely collected clinical data at antenatal booking	Stillbirths and neonatal deaths during delivery hospitalization	**Adjusted OR for perinatal mortality (95% CI):** • Continued smoking vs. nonsmoker: 1.36 (0.99–1.87) • Quit smoking vs. continued smoking: 0.78 (0.28–2.16)	Results adjusted for plurality, previous pregnancy complications, parity, and ethnicity Did not account for alcohol or substance use
Bailey (2015)	• Randomized clinical trial of smoking cessation intervention • n = 1,486 • 2008–2012 • Tennessee	• Quit smoking: Smoked at first prenatal visit but quit by third trimester • Continued smoking: Smoked at first prenatal visit and still smoking during third trimester • Smoking history based on self-reports obtained at first prenatal visit • Quit status ascertained during third trimester by exhaled CO and urine cotinine and by self-reports at delivery	Fetal or neonatal demise not defined	**Percentage perinatal deaths:** • Quit smoking: 0.2% • Continued smoking: 1.0% • p = 0.046	Randomized cessation trial and thus no comparison group of never smokers Results adjusted for maternal age, education, marital status, insurance status, and marijuana use Examined alcohol use, but not significant in the model

Notes: **CI =** confidence interval; **CO =** carbon monoxide; **OR =** odds ratio.

(Table 4.37). One study examined cessation with respect to individual pregnancies (Wisborg et al. 2001), and two examined cessation across two consecutive pregnancies (Abrevaya 2008; Johansson et al. 2009). All three studies relied on self-reported smoking status and adjusted for multiple potential confounders, with one also adjusting for alcohol use (Wisborg et al. 2001), but none adjusted for substance use. In a prospective cohort study of Danish women, Wisborg and colleagues (2001) found that, compared with women who did not smoke at all during pregnancy, women who smoked during pregnancy but quit by the time of the first antenatal interview (around 16 weeks' gestation) had no significant increase in the risk of infant death (aOR = 1.0; 95% CI, 0.5–1.9). Johansson and colleagues, who examined smoking status at the first antenatal visit in two consecutive pregnancies, found no increase in infant mortality for the second pregnancy among women who were light smokers in the first pregnancy but had quit by the second pregnancy compared with women who did not smoke in either pregnancy (aOR = 1.0; 95% CI, 0.8–1.5). This study, however, found increased risk in women who were heavy smokers in the first pregnancy and quit by the second pregnancy (aOR = 1.4; 95% CI, 1.0–2.0). Similarly, heavy smokers who smoked only in the second pregnancy had a significantly increased risk of infant mortality for that pregnancy (aOR = 1.8; 95% CI, 1.0–2.9). In the third study, Abrevaya and colleagues (2008) found no significant difference in the risk of infant mortality during the second pregnancy in women who smoked during the first but not the second pregnancy compared with women who smoked during both pregnancies. Comparisons between women who quit smoking by the second pregnancy and women who did not smoke in either pregnancy were not reported.

Summary of the Evidence

Since the 2004 Surgeon General's report (USDHHS 2004), few studies have addressed smoking cessation and infant mortality, and findings have been mixed. The evidence is inadequate to infer that women who quit smoking before or during early pregnancy have reduced risk for infant mortality compared with continuing smokers.

Female Reproductive Health

Fertility

"Infertility" is defined as the inability to achieve pregnancy following 12 months of regular, unprotected sexual intercourse (Practice Committee of American Society for Reproductive Medicine [PCASRM] 2013), while "fecundity" refers to the biologic ability to conceive. Subfertility is any form of reduced fertility in couples trying to conceive. Up to 15% of couples have some form of infertility (Thoma et al. 2013), approximately half of which is related to female causes, 30% to male causes, and 20% to both male and female causes (Kovac et al. 2015). Women can have primary infertility (inability to conceive and no previous pregnancies), or secondary infertility (inability to conceive following a previous pregnancy). The PCASRM (2012) has estimated that 13% of infertility may be attributable to smoking.

Several pathways involved in reproduction could be targets of toxicants in cigarette smoke that adversely affect fertility (Dechanet et al. 2011; Marom-Haham and Shulman 2016). Cigarette smoking could affect folliculogenesis by inhibiting the growth of follicles or the maturation of oocytes. Possible mechanisms include abnormal oxidative stress, increased apoptosis, abnormal cross talk between oocytes and granulosa cells by inhibition of gap-junction formation between cells, or impairment of oocyte nuclear function by damaging DNA or interfering with meiosis. In addition, compounds in cigarette smoke could disrupt steroidogenesis, leading to alterations of estrogens and/or androgens in the follicular environment. Cigarette smoke, through its proangiogenic or antiangiogenic properties, could affect the early development of the embryo. Additionally, cigarette smoke could target the oviduct (by acting on its adhesive properties, ciliary activity, or muscular contractions) or the endometrium (by impairing endometrial proliferation or maturation, or by causing aberrant regulation of angiogenesis). Finally, tobacco smoke could cause vascular impairment in the uterine arteries or could affect myometrial contractility, which could adversely affect implantation (Dechanet et al. 2011; Marom-Haham and Shulman 2016).

The 1990 Surgeon General's report found evidence that cessation before attempted conception restored the fertility of former smokers to that of never smokers (Baird and Wilcox 1985; Daling et al. 1985; Howe et al. 1985; USDHHS 1990). The 2001 Surgeon General's report reviewed conception delay and infertility and found that although active smoking was associated with conception delay, the effect appeared to be reversible, as several studies observed similar conception rates for former and never smokers (USDHHS 2001). The report noted that smoking was consistently associated with impaired fertility in both case-control and cohort studies, and some studies found evidence of a dose-response relationship. Former smokers appeared to have little excess risk of impaired fertility. The report also concluded that smokers are at increased risk of primary and secondary infertility, but it did not draw conclusions about smoking cessation (USDHHS 2001).

The 2004 Surgeon General's report reviewed studies of smoking and fertility in women and found consistent

Table 4.37 Studies on smoking cessation and infant mortality

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Wisborg et al. (2001)	• Prospective cohort study • Singleton pregnancies • n = 25,102 • 1989–1996 • Denmark	• Nonsmokers: Not smoking at time of either antenatal interview • Quit smoking: Smoked during pregnancy but quit by first antenatal interview • Continued smoking: Smoked ≥1 cigarette/day at first antenatal interview • Smoking status ascertained from maternal interviews conducted before first antenatal visit (typically 16 weeks' gestation) and before the 30-week antenatal visit	Death of a liveborn infant before 1 year of age	**Crude and adjusted OR for infant mortality (95% CI):** • Nonsmokers (reference) • Quit smoking: – Unadjusted: 1.0 (0.5–1.9) – Adjusted: 0.9 (0.5–1.9)	Results adjusted for parity; maternal age, education, employment, caffeine and alcohol intake, weight, and height; and sex of the infant Did not account for substance use
Abrevaya et al. (2008)	• Population-based, retrospective cohort study using Michigan-linked certificates of live births • First and second pregnancies in which women smoked during the first pregnancy • n = 14,731 (18–24 years of age) • n = 8,044 (25–30 years of age) • 1989–2004 • Michigan	• Quit smoking: Smoked during first pregnancy but not during second pregnancy • Continued smoking during both pregnancies: Smoked during first and second pregnancies • Smoking status based on smoking history collected from certificates of live birth, which used one question on tobacco use during pregnancy (yes/no)	Death of a liveborn infant within 1 year of birth	**Adjusted OR for infant mortality (95% CI):** • Quit smoking (reference) • Continued smoking during both pregnancies: – 18–24 years of age: 1.07 (0.71–1.61) – 25–30 years of age: 0.67 (0.28–1.62)	Results adjusted for maternal race, education, income, population, interpregnancy interval, year of birth, trimester of first prenatal visit, presence of father's name on birth certificate, number of prenatal visits, and first-birth value of the outcome Did not account for alcohol or substance use

Table 4.37 Continued

Study	Design/population	Exposure groups/how determined	Outcome definition	Findings	Comments
Johansson et al. (2009)	• Births from the Swedish Birth Register • First and second singleton pregnancies • n = 555,046 • Sweden	• Nonsmokers: Not smoking at first antenatal visit in either pregnancy • Quit smoking: Smoked at first antenatal visit of first pregnancy but not at first antenatal visit of second pregnancy • Relapsed: Did not smoke at first antenatal visit of first pregnancy but smoked at first antenatal visit of second pregnancy • Continued smoking: Smoked at first antenatal visit of both pregnancies: – Light smoker: 1–9 cigarettes/day – Heavy smoker: ≥10 cigarettes/day • Smoking status based on maternal self-reports obtained at first antenatal visit and on Swedish Birth Register	Death during the first year of life in a liveborn infant from second pregnancy, born ≥22 weeks' gestation	**Adjusted OR for infant mortality after second pregnancy (95% CI):** • Nonsmoker (reference) • Quit smoking: – Light smoker, first pregnancy: 1.0 (0.8–1.5) – Heavy smoker, first pregnancy: 1.4 (1.0–2.0) • Relapsed: – Light smoker, second pregnancy: 1.1 (0.8–1.5) – Heavy smoker, second pregnancy: 1.8 (1.0–2.9) • Continued smoking (results attenuated when also adjusted for gestational age and placental abruption; remained significant for all but light/light smokers): – Light/light: 1.3 (1.1–1.6) – Heavy/light: 1.5 (1.1–1.9) – Light/heavy: 1.7 (1.3–2.2) – Heavy/heavy: 2.0 (1.7–2.4)	Results adjusted for maternal age, education, country of birth, interpregnancy interval, and year of delivery Did not account for alcohol or substance use

Notes: **CI =** confidence interval; **OR =** odds ratio.

evidence that smoking reduces fecundity and increases the risk of primary infertility, with some evidence presented of a dose-response relationship with the number of cigarettes smoked. The report concluded that a causal relationship exists between smoking and reduced fertility in women, but it did not draw conclusions related to cessation (USDHHS 2004). The 2010 Surgeon General's report provided an updated review of smoking and fertility in women, including a meta-analysis of 12 studies that calculated an overall OR of 1.6 (95% CI, 1.3–1.9) for infertility versus nonsmokers (Augood et al. 1998). Earlier, a meta-analysis of data from seven studies of in vitro fertilization (IVF) patients indicated a significant reduction in conceptions per cycle in smokers compared with nonsmokers (OR = 0.57; 95% CI, 0.42–0.78) (Hughes and Brennan 1996). A subsequent review of 22 studies reported that 19 found evidence of adverse effects of smoking on female reproduction (Wilks and Hay 2004).

Since 2000, two papers have examined smoking cessation and fertility in women. In a study of 569 women who became pregnant without infertility treatment, Munafò and colleagues (2002) found that women who smoked in the year before conception took approximately 2 months longer to conceive than women who quit at least a year before conception. In multivariable models that adjusted for age, weight, lifetime use of oral contraceptives, alcohol consumption, and vigorous exercise, the number of pack-years of smoking was not associated with time to conception among former smokers (p = 0.093), but the number of cigarettes smoked per day was associated with increased time to conception among women who smoked during the period in which they were trying to conceive.

Radin and colleagues (2014) examined the association between fecundability (the probability of becoming pregnant in a single menstrual cycle), duration of active smoking, and smoking cessation in a prospective cohort of women in Denmark who were 18–40 years of age. The women were followed for up to 12 cycles after beginning to attempt conception. Overall, former smokers, occasional smokers, and regular smokers did not differ in fecundability from never smokers in models that adjusted for age, partner smoking, passive smoking, and the number of cycles at risk (adjusted fecundability ratios [aFRs] = 0.99, 1.11, and 0.89, respectively). Former smokers with at least 10 pack-years of smoking, however, had significantly reduced fecundability (aFR = 0.74).

Summary of the Evidence

The current review confirms findings of previous Surgeon General's reports that support a causal association between smoking and reduced fertility (USDHHS 2001, 2004). Although past reports of the Surgeon General found a causal association between smoking and reduced fertility and suggestive evidence of restored fertility after smoking cessation, studies published since 2000 do not provide sufficient evidence to build upon the findings of the previous reports. Recent evidence is inadequate to further elucidate the association between smoking cessation or the timing of cessation and attempted conception and improved fecundability. The evidence is inadequate to elucidate the association between smoking cessation or the timing of cessation and fertility or fecundity.

Age at Menopause

The age of natural menopause is defined as the age menses cease for 12 consecutive months with no obvious cause, such as pregnancy or lactation, and it may be an important predictor of subsequent morbidity and mortality. The risks of cardiovascular disease and osteoporosis are higher for women with earlier menopause, but their risk of breast cancer is reduced (Gold 2011). Age at menopause was found to be associated with increased all-cause mortality when women with natural menopause before 40 years of age were compared with those who experienced menopause at 50 years of age or older (Gold 2011). Earlier, a large international study of women from 11 countries found the median age at menopause to be 50 years (range: 49–52 years across the countries) (Morabia and Costanza 1998). Factors associated with earlier menopause in epidemiologic studies include non-White race, low socioeconomic status, nulliparity, never using oral contraceptives, and lower weight (Gold 2011). Mechanisms contributing to an effect of smoking on age at menopause could involve genetics, environmental exposures, hormonal pathways, and health status (Gold et al. 2001, 2011; He and Murabito 2014; Sapre and Thakur 2014; Schoenaker et al. 2014).

The 1990 Surgeon General's report noted that cigarette smoking has consistently been associated with earlier menopause in epidemiologic studies (USDHHS 1990). The report found that smokers experience menopause 1 to 2 years earlier than nonsmokers and that the consistency of study findings and evidence for a dose-response relationship supported a causal association. The report also noted that the age of menopause in former smokers appeared to be closer to that in never smokers than in current smokers, suggesting that the effects of smoking on age at menopause may be at least partially reversible (USDHHS 1990). The data at that time were found to be limited, however, with few studies examining the duration of cessation or lifetime tobacco exposure.

The 2001 Surgeon General's report found that smoking was consistently associated with a 1- to 2-year decrease in age at natural menopause and concluded that smokers have a younger age at natural menopause than nonsmokers (USDHHS 2001). Possible mechanisms addressed in that report included exposure of the

ovaries to toxic components in tobacco smoke (animal studies suggest that tobacco smoke may cause follicular atresia) and the effects of nicotine on the metabolism of sex hormones. Although the report did not draw conclusions on smoking cessation, it did summarize studies that included former smokers (USDHHS 2001); those studies had mixed results.

Just over a decade after the 2001 Surgeon General's report, a meta-analysis of 11 papers published between 1997 and 2009 (comprising about 50,000 women) found that smoking was significantly associated in all the studies with earlier age at natural menopause (Sun et al. 2012). After adjustment for heterogeneity, the OR for onset of earlier menopause was 0.67 (95% CI, 0.61–0.73), and menopause was estimated to take place an average of approximately 1 year earlier in smokers compared with nonsmokers. Results from some of the studies supported the notion that the timing of menopause may be dependent on the amount of cigarettes smoked and/or the duration of smoking. Kinney and colleagues (2006) analyzed longitudinal data from almost 500 women and found that a change in age of menopause was observed only among active smokers who smoked more than 14 cigarettes per day or who had accumulated at least 20 pack-years. Those authors found no association between menopause and previous smoking, even among women who had smoked more than 14 cigarettes per day, smoked more than 10 pack-years, or who had quit smoking within the past decade (Kinney et al. 2006). Similarly, Blanck and colleagues (2004) found that in a study of 874 women, menopause came earliest among current smokers who started smoking in their teens, smoked at least 20 cigarettes per day, smoked for 10 to 19 years, or had at least 10 pack-years. Former smokers and never smokers did not differ in time to menopause, however, even after adjusting for number of term pregnancies and education (Blanck et al. 2004).

In a study of more than 5,500 women, Van Asselt and colleagues (2004) found that although there was a significant association between current smoking and earlier age of menopause (rate ratio = 1.41; 95% CI, 1.32–1.50), there was no association with former smoking (rate ratio = 0.95; 95% CI, 0.89–1.02). The latter was true regardless of the number of years since cessation. In a more recent study of more than 2,000 women, Mikkelsen and colleagues (2007) found that—after adjusting for marital status, education level, social participation, health status, and coffee consumption—women who stopped smoking more than 10 years before menopause were significantly less likely to have an early menopause (<45 years of age) (aOR = 0.13; 95% CI, 0.05–0.36) than women who were current smokers (aOR = 1.59; 95% CI, 1.11–2.28). Finally, in one of the few longitudinal studies of smoking status and menopause, Hayatbakhsh and colleagues (2012) followed more than 3,500 Australian women and found that women smoking at the 21-year follow-up were 61% more likely to experience menopause before 45 years of age than women who had never smoked (adjusted hazard ratio [HR] = 1.61; 95% CI, 1.27–2.04), even after adjusting for education, ethnicity, BMI, use of oral contraceptives, and gravidity. Those who quit smoking before the 14-year follow-up assessment had a risk of early menopause that was the same as that of never smokers, while those who quit later (between 14 and 21 years of follow-up) may have been at increased risk (HR = 1.36; 95% CI, 0.89–2.07). Among those smoking at the 14-year follow-up, only smoking more than 20 cigarettes per day was significantly associated with early menopause.

Menopause is associated with the exhaustion of the ovarian follicular pool (Vermeulen 1993; Hacker et al. 2015), and it has been hypothesized that smoking could alter the timing of menopause by hastening the decline of ovarian reserves. Evidence for this pathway (Richardson et al. 2014) includes studies demonstrating an increased concentration of follicular-stimulating hormone (FSH) in smokers compared with nonsmokers (Cooper et al. 1995) and a reduced number of oocytes retrieved in IVF cycles in smokers compared with nonsmokers (Zenzes et al. 1997; El-Nemr et al. 1998; Fuentes et al. 2010). The mechanisms underlying the potential effects of tobacco smoke on ovarian reserves are not well understood, but they could include direct effects on gametes or effects on ovarian vascularization (Richardson et al. 2014). A mechanism involving depletion of ovarian reserves would likely result in an irreversible effect on age at menopause.

It has also been hypothesized that antiestrogenic effects of environmental toxicants, such as those found in tobacco smoke, could contribute to earlier age at menopause (Gu et al. 2013). Potential pathways include inhibition of estrogen biosynthesis, induction of the 2-hydroxylation pathway, and competitive binding of estrogen receptors or sex hormone-binding globulin (Baron et al. 1990). Gu and colleagues (2013), who used luteal phase urine samples from 603 premenopausal women in the Nurses' Health Study II to study specific pathways, found lower total estrogen and estrogen metabolites and parent estrogens in current smokers compared with never smokers (with statistically significant differences for estradiol), suggesting that cigarette smoking reduces the biosynthesis of estrogen and induces estrogen metabolism. No differences were seen in levels of individual estrogen metabolites, metabolic pathway groups, or pathway ratios between never and former smokers (most of whom had quit more than 5 years earlier), suggesting that the effects of smoking on estrogen biosynthesis may be reversible. The authors were unable to

examine whether components of tobacco smoke bind estrogen receptors or sex hormone-binding globulin.

Summary of the Evidence

The 2001 Surgeon General's report found that "[w]omen smokers have a younger age at natural menopause than do nonsmokers and may experience more menopausal symptoms" (USDHHS 2001, p. 14). Several papers published since the 2001 report provide additional evidence that active smoking results in earlier age at menopause. Several of these recent papers also examined risk in former smokers and found no evidence of earlier age at menopause, suggesting that the mechanisms through which smoking affects age at menopause are at least partially reversible. However, uncertainty remains regarding the role of the duration and amount of smoking in former smokers, and these variables were categorized differently across studies. Therefore, the evidence is suggestive but not sufficient to conclude that cessation reduces the risk of earlier menopause compared with continued smoking, and uncertainty remains regarding the contributions to the risk of earlier menopause of age at cessation, the number of years smoked, the number of cigarettes smoked per day, and the number of pack-years smoked in former smokers.

Male Reproductive Health

Fertility and Sperm Quality

The 1990 Surgeon General's report found few studies about sperm quality after smoking cessation, and those studies had serious limitations (USDHHS 1990). The 2004 Surgeon General's report concluded that the evidence was inadequate to infer the presence or absence of a causal relationship between active smoking and sperm quality, but the evidence did suggest that smokers have decreased semen volume and increased abnormal morphologic forms (USDHHS 2004). The clinical relevance of these findings, however, was uncertain. The 2010 Surgeon General's report, which also reviewed sperm quality and male fertility, noted that studies conducted after the 2004 report strengthened the evidence that smoking affects semen quality and fertility (USDHHS 2010). The 2010 report reviewed potential mechanisms, including alterations in the hormonal milieu, effects on the sperm plasma membrane, and damage to DNA and/or chromosomes in sperm. The report also noted that (a) studies designed to address the timing of exposure in relation to the maturation of sperm cells had not been conducted and (b) the effects of tobacco smoke on spermatogonial stem cells could cause long-term effects that could persist after smoking cessation, while effects on both epididymal sperm and mature sperm could be reversible (USDHHS 2010). The report also noted that studies examining hormone levels in male smokers and nonsmokers found inconsistent results and variation in how obesity was considered (obesity is associated with the conversion of androgens to estrogen) and in the type of circulating hormones studied (free or bioavailable levels). The report found consistent evidence linking smoking in men to chromosomal changes and DNA damage in sperm, which affects male fertility, pregnancy viability, and anomalies in offspring.

Among the studies published after the 2010 Surgeon General's report was a meta-analysis of 20 studies comprising more than 5,800 men, with the authors' finding that cigarette smoking was associated with reduced sperm count, lower motility, and changes in morphology (Sharma et al. 2016). Elsewhere, in a small study of 136 men that excluded those with known infertility, levels of testosterone, luteinizing hormone, and prolactin were higher in smokers (≥5 cigarettes/day) than never smokers, but there were no differences in these measures between former smokers and never smokers (Blanco-Munoz et al. 2012). In another study, Santos and colleagues (2011) evaluated sperm quality after participation in a 3-month smoking cessation program. A man in the study had smoked about 30 cigarettes per day for about 13 years and had secondary infertility. The monitoring found an improvement in his sperm count (from 28.6 to 72.2 million/ejaculate) and motility (32.7% to 78.8%) but no changes in sperm DNA fragmentation, number of germinal cells, or morphology. In addition, the percentage of sperm tails increased with tyrosine-phosphorylated proteins and the number of rapid spermatozoa recuperated after an enrichment technique, suggesting that the transduction signals necessary for proper motility and capacitation were improved. Finally, a study of rats found that both the motility and amount of sperm decreased significantly with exposure to nicotine, and that this was accompanied by reduced fertility; declines were ameliorated by the cessation of nicotine exposure in the male rats (Oyeyipo et al. 2011).

Summary of the Evidence

Little new evidence published since the 2010 Surgeon General's report has addressed whether the effects of smoking on male fertility and sperm quality are reversible with cessation. Therefore, the evidence is inadequate to determine whether smoking cessation reduces the effects of smoking on male fertility and sperm quality.

Erectile Dysfunction

"Erectile dysfunction" (ED) is defined as the persistent inability of a male to attain and maintain an erection

adequate for satisfactory sexual performance (National Institutes of Health Consensus Development Panel on Impotence 1993). Using data from the National Health and Nutrition Examination Survey of 2001–2002, Selvin and colleagues (2007) estimated that 18.4% of U.S. men 20 years of age or older had ED, or 18 million nationwide. Globally, 322 million men may be affected by the year 2025.

The 1990 Surgeon General's report found that smoking may be associated with impaired male sexual performance, but because the data were limited, no conclusions could be drawn regarding the relationships between smoking cessation and sexual performance or the surrogate penile brachial index, which is calculated as the systolic blood pressure in the penis divided by the systolic blood pressure in the arm (USDHHS 1990). The 2014 Surgeon General's report found the evidence sufficient to infer a causal relationship between smoking and ED. This conclusion was on the basis of consistent findings of smoking as a risk factor for ED across both cross-sectional and prospective population-based cohort studies. These studies confirmed the appropriate temporality of the association and evidence of a dose-response relationship between the magnitude of the risk and the level of exposure. Potential mechanisms were also reviewed in the 2014 Surgeon General's report and included the effects of nicotine on the dynamics of blood flow required for erection (nicotine induces vasospasm in the penile arteries); formation of atherosclerotic lesions in the penile arteries; degenerative changes in the penile tissue, such as decreases in smooth muscle, sinusoidal endothelium, nerve fibers and capillaries, and increased collagen density; reduced endothelium-derived production of nitric oxide in the vasculature of the penis; adverse effects on vascular medial elastic fibers; and oxidative injury due to the production of superoxide radicals in the cavernosal smooth muscle cells (USDHHS 2014).

The 2014 Surgeon General's report also addressed smoking cessation, although that report did not draw related conclusions. The report reviewed selected results from two population-based studies (the Vietnam Experience Study of 1985–1986 and the prospective Massachusetts Male Aging Study) against findings that smoking cessation leads to recovery of erectile function (Mannino et al. 1994; Feldman et al. 2000; USDHHS 2014). However, the Massachusetts Male Aging Study, which followed quitters for nearly 9 years, did not show evidence that the incidence of ED was reduced after cessation (Feldman et al. 2000). In that study, however, participants had started smoking at an early age (mean age: 16.6 years) and had a substantial lifetime exposure (mean pack-years: 39.4), so that results could not be generalized to populations with lower levels of tobacco exposure (Feldman et al. 2000). Notably, a separate analysis of the Massachusetts Male Aging Study found that cessation appeared to protect against the progression of ED but had little effect on remission (Travison et al. 2007).

Experimental studies of the acute effects of short-term smoking cessation reviewed in the 2014 Surgeon General's report show that cessation may result in improvements in erectile function. For example, Glina and colleagues (1988), who monitored intracavernous pressure after pharmacologic stimulation in 12 smokers on a day of abstinence and after smoking two cigarettes, found that all participants obtained an erection on days of abstinence, but only four smokers did so on days of smoking cigarettes (Glina et al. 1988). Later, Sighinolfi and colleagues (2007), who studied 20 chronic smokers with ED using penile color Doppler ultrasonography after pharmacostimulation at baseline and after 24 to 36 hours of abstinence from smoking, also achieved positive results. At baseline, 50% of these smokers had abnormal peak systolic velocity and 75% had abnormal end diastolic velocity, but at 24 to 36 hours, none had abnormal peak systolic velocity and just 15% had abnormal end diastolic velocity. Finally, in a sample of 10 current, long-term smokers, cessation for 24 hours significantly improved nocturnal penile tumescence and rigidity (Guay et al. 1998).

Table 4.38 presents seven cross-sectional studies of risk of ED in former smokers that were not reviewed in the 2014 Surgeon General's report. Six of the seven studies found a higher prevalence of ED among both former and continuing smokers (range in aOR for former smokers relative to never smokers: 1.3–2.15) (Bortolotti et al. 2001; Mirone et al. 2002; Safarinejad 2003; Austoni et al. 2005; Chew et al. 2009), but the associations for both former and current smokers did not reach significance in one study (Shiri et al. 2005). One study reported an aOR of less than 1.0 for former smokers (Lam et al. 2006), but this result was not statistically significant.

In a study of 1,580 men, Chew and colleagues (2009) found that both former and current smokers were at higher risk of ED compared with never smokers (overall aOR = 1.3 and 1.6, respectively, adjusted for age and symptomatic cardiovascular disease, including hypertension, ischemic heart disease, peripheral arterial disease, and stroke), but by age group, associations between former or current smoking and ED were significant only among men 50 years of age and older. Similarly, in a study of 2,010 men, Mirone and colleagues (2002) found that current smokers and former smokers had similar aORs for ED (1.7 and 1.6, respectively, adjusted for age and education); those researchers also found that smoking for more than 20 years increased the odds of ED compared with smoking for 20 years or less (aOR = 1.6 and 1.2, respectively). The increased risk was limited to current and former smokers without chronic medical conditions (aOR = 1.7–2.4 for current smokers without medical conditions, 0.4–1.2 for

Table 4.38 Studies on smoking cessation and erectile dysfunction

Study[a]	Design/population	Reference	Results: Adjusted OR (95% CI)	Comments
Bortolotti et ak, (2001)	• Cross-sectional • Men with diabetes • n = 9,670 • 1996 • Italy	Never smokers	• Former smokers: 1.5 (1.3–1.6)[b] • Current smokers: 1.4 (1.3–1.6)[b]	Former smoker if quit more than 1 year before survey; adjusted for age
Mirone et al. (2002)	• Cross-sectional • n = 2,010 • 1996–1997 • Italy	Never smokers	• Former smokers: 1.6 (1.1–2.3)[b] • Current smokers: 1.7 (1.2–2.4)[b]	Former smoker if quit more than 1 year before survey; adjusted for age and education
Safarinejad (2003)	• Population-based, cross-sectional • Men 20–70 years of age • n = 2,444 • Year: Not reported • Iran	Never smokers	• Former smokers: 2.15 (1.38–3.1)[b] • Current smokers: 2.41 (1.52–3.30)[b]	Adjusted for age
Austoni et al. (2005)	• Cross-sectional • Men attending free andrologic consultations • n = 16,724 • 2001–2002 • Italy	Never smokers	• Former smokers: – Overall: 1.3 (1.2–1.5)[b] – Smoked <10 years: 1.0 (0.6–1.7) – Smoked 10–20 years: 1.2 (0.8–1.8) – Smoked >20 years: 2.0 (1.3–2.0)[b] • Current smokers: – <10 cigarettes/day: 1.0 (0.9–1.2) – ≥10 cigarettes/day: 1.4 (1.2–1.5)[b] – Smoked <10 years: 1.1 (0.7–1.6) – Smoked 10–20 years: 1.7 (1.2–2.3)[b] – Smoked >20 years: 1.6 (1.3–2.0)[b]	Former smoker if quit more than 1 year before survey; adjusted for age, marital status, education, BMI, physical activity, and chronic diseases
Shiri et al. (2005)	• Population-based, cross-sectional analysis within prospective cohort • Men 50, 60, or 70 years of age in 1994 • n = 1,442 • 1994 • Finland	Never smokers	• Former smokers: 1.3 (0.9–1.8) • Current smokers: 1.4 (0.9–2.2)	Adjusted for age, education, marital status, and alcohol consumption
Lam et al. (2006)	• Population-based, cross-sectional • Men 31–60 years of age • n = 819 • 2001 • Hong Kong	Never smokers	• Former smokers: 0.93 (0.60–1.45) • Current smokers: – <20 cigarettes/day: 1.02 (0.69–1.51) – ≥20 cigarettes/day: 1.47 (1.00–2.16)[b]	Erectile dysfunction defined as sexual dissatisfaction and/or erectile difficulty; adjusted for age

Table 4.38 Continued

Study[a]	Design/population	Reference	Results: Adjusted OR (95% CI)	Comments
Chew et al. (2009)	• Population-based, cross-sectional • n = 1,580 • 2001–2002 • Australia	Never smokers	• Former smokers: – Overall: 1.33 (0.95–1.87) – Quit ≤5 years: 1.22 (0.67–2.22) – Quit 6–10 years: 2.26 (1.09–4.70)[b] – Quit >10 years: 1.32 (0.92–1.89) – <50 years of age: 1.18 (0.61–2.31) – ≥50 years of age: 2.56 (1.42–4.58)[b] • Current smokers: – Overall: 1.57 (1.02–2.42)[b] – 1–10 cigarettes/day: 1.30 (0.69–2.44) – 11–20 cigarettes/day: 1.69 (0.79–3.64) – >20 cigarettes/day: 1.57 (0.74–3.34) – <50 years of age: 0.82 (0.40–1.69) – ≥50 years of age: 1.47 (0.99–2.18)	Adjusted for age and symptomatic cardiovascular disease, including hypertension, ischemic heart disease, peripheral arterial disease, and stroke

Notes: **BMI =** body mass index; **CI =** confidence interval; **OR =** odds ratio.

[a]Measure of association adjusted for covariate(s).

[b]$p < 0.05$.

current smokers with medical conditions; and aOR = 1.4–1.7 for former smokers without medical conditions, 0.4–1.2 for former smokers with medical conditions). Among former smokers, the risk of ED was not clearly associated with the number of years since cessation.

In a large study with more than 16,000 participants, Austoni and colleagues (2005) found associations between smoking and ED that were similar for current smokers smoking more than 10 cigarettes per day and former smokers compared with never smokers (aOR = 1.4; 95% CI, 1.2–1.5, and aOR = 1.3; 95% CI, 1.2–1.5, respectively, adjusted for age, marital status, education, BMI, physical activity, and chronic diseases). There was no increased risk for men who smoked 10 or fewer cigarettes per day, but the risk of ED increased with duration of smoking for both current and former smokers. When stratified by the presence or absence of medical conditions (hypertension, cardiovascular disease, diabetes, and hypercholesterolemia), aORs were similar for those with and without each condition in former smokers, and all associations were significant except for former smokers with hypercholesterolemia (aOR = 1.2; 95% CI, 0.9–1.6). Earlier, in a sample of nearly 10,000 men with diabetes, Bortolotti and colleagues (2001) found that both former smokers and current smokers had a higher risk of ED relative to never smokers (aOR = 1.5; 95% CI, 1.3–1.6 and aOR = 1.4; 95% CI, 1.3–1.6, respectively, results adjusted for age). Increased time since cessation was not clearly associated with reduced risk of ED among former smokers.

In a prospective study of more than 1,400 men 50–75 years of age, Shiri and colleagues (2005) observed elevated but nonsignificant aORs for ED among former and current smokers at baseline (1.3; 95% CI, 0.9–1.8, and 1.4; 95% CI, 0.9–2.2, respectively, adjusted for age, education, marital status, and alcohol consumption) but did not find a dose-response relationship in current smokers with duration of smoking or in former smokers with the number of years of smoking (not shown in table). In a follow-up survey conducted 5 years later, spontaneous recovery was not significantly associated with being a former smoker (aOR = 0.7; 95% CI, 0.3–1.3). When the sample was limited to men without ED at baseline in 1994, smokers who developed vascular disease by 1999 had a 3-fold greater risk of developing ED by 2004 (adjusted incidence density ratio = 3.1; 95% CI, 1.3–7.5; covariates included age, education, marital status, diabetes, depression, BMI, and alcohol consumption) compared with men who never smoked and did not develop vascular disease (men included in the final model were not specified) (Shiri et al. 2006). In contrast, smokers who did not develop vascular disease did not have an increased risk of ED. Former smokers were not at increased risk for ED, independent of vascular disease. Finally, in a prospective study of almost 300 smokers seeking smoking cessation services who reported having symptoms of ED with onset more than 5 years after initiating smoking, Pourmand and colleagues (2004) found that at 1-year follow-up, ED status improved by at least one grade in 25% of former smokers but such improvement was not observed among continuing smokers (results of statistical testing not presented).

Summary of the Evidence

Cross-sectional studies consistently found that former smokers had an increased prevalence of ED relative to never smokers, and in some instances, prevalence was similar to that of current smokers. In contrast, results of prospective studies were mixed, with some showing no increased risk of ED in former smokers compared with never smokers, and others showing increased risk. Experimental studies of short-term cessation suggest that such cessation is associated with acute improvements in erectile function. Limited data suggest that smoking contributes to ED at least in part through its effects on the risk of vascular disease. Smoking likely has both reversible (such as nicotine-induced vasospasm of penile arteries) and irreversible (such as degenerative tissue changes) effects on erectile function, complicating interpretation of data across different study designs. Changes in risk of ED by duration or intensity of smoking could further complicate the interpretation of data. Therefore, the evidence is inadequate to determine whether smoking cessation reduces the risk of ED compared with continued smoking. The evidence is suggestive but not sufficient to conclude that former smokers are at increased risk of ED compared with never smokers.

Synthesis of the Evidence

Smoking has diverse adverse effects on the reproductive health of females and males. This review has found numerous health benefits of cessation for women and their fetuses and newborns. For males, evidence of the reproductive health benefits (e.g., enhancing sperm quality and functionality, avoiding erectile dysfunction) of cessation is more limited.

Conclusions

1. The evidence is sufficient to infer that smoking cessation by pregnant women benefits their health and that of their fetuses and newborns.

2. The evidence is inadequate to infer that smoking cessation before or during early pregnancy reduces

the risk of placental abruption compared with continued smoking.

3. The evidence is inadequate to infer that smoking cessation before or during pregnancy reduces the risk of placenta previa compared with continued smoking.

4. The evidence is inadequate to infer that smoking cessation before or during pregnancy reduces the risk of premature rupture of the membranes compared with continued smoking.

5. The evidence is inadequate to infer that smoking during early or mid-pregnancy alone, and not during late pregnancy, is associated with a reduced risk of preeclampsia.

6. The evidence is sufficient to infer that women who quit smoking before or during pregnancy gain more weight during gestation than those who continue to smoke.

7. The evidence is suggestive but not sufficient to infer that women who quit smoking before or during pregnancy gain more weight during gestation than nonsmokers.

8. The evidence is inadequate to infer that smoking cessation during pregnancy increases the risk of gestational diabetes.

9. The evidence is sufficient to infer that smoking cessation during pregnancy reduces the effects of smoking on fetal growth and that quitting smoking early in pregnancy eliminates the adverse effects of smoking on fetal growth.

10. The evidence is inadequate to determine the gestational age before which smoking cessation should occur to eliminate the effects of smoking on fetal growth.

11. The evidence is sufficient to infer that smoking cessation before or during early pregnancy reduces the risk for a small-for-gestational-age birth compared with continued smoking.

12. The evidence is suggestive but not sufficient to infer that women who quit smoking before conception or during early pregnancy have a reduced risk of preterm delivery compared with women who continue to smoke.

13. The evidence is suggestive but not sufficient to infer that the risk of preterm delivery in women who quit smoking before or during early pregnancy does not differ from that of nonsmokers.

14. The evidence is inadequate to infer that smoking cessation during pregnancy reduces the risk of stillbirth.

15. The evidence is inadequate to infer that smoking cessation during pregnancy reduces the risk of perinatal mortality among smokers.

16. The evidence is inadequate to infer that women who quit smoking before or during early pregnancy have a reduced risk for infant mortality compared with continued smokers.

17. The evidence is inadequate to infer an association between smoking cessation, the timing of cessation, and female fertility or fecundity.

18. The evidence is suggestive but not sufficient to infer that smoking cessation reduces the risk of earlier age at menopause compared with continued smoking.

19. The evidence is inadequate to infer that smoking cessation reduces the effects of smoking on male fertility and sperm quality.

20. The evidence is suggestive but not sufficient to infer that former smokers are at increased risk of erectile dysfunction compared with never smokers.

21. The evidence is inadequate to infer that smoking cessation reduces the risk of erectile dysfunction compared with continued smoking.

Implications

As with previous reports, the evidence presented in this section reaffirms that cigarette smoking cessation before and during pregnancy reduces the adverse effects of smoking on fetal growth, including risk for being small for gestational age and low birth weight. The timing of the cessation and its beneficial effects are consistent with fetal growth patterns, which accelerate during the third trimester; thus, quitting early in pregnancy obviates the birth weight reduction that results from smoking throughout pregnancy. The evidence also suggests that smoking cessation may reduce the risk of other adverse outcomes, including placental abruption, preterm delivery, stillbirth, and early menopause. If smoking cessation reduces the

risk of such pregnancy complications as placental abruption and preterm delivery, then reductions in such downstream outcomes as stillbirths and perinatal and neonatal mortality would also be expected. More research on the timing of cessation with respect to pregnancy onset is needed to determine how to maximize improvements in pregnancy outcomes for women and infants.

Prenatal smoking cessation has substantial health benefits for mothers and offspring, but the evidence summarized in this section also provides some support that selected adverse outcomes might also be increased with smoking cessation. For example, increased gestational weight gain associated with cessation could potentially increase the percentage of women who exceed recommended gestational weight gain and experience associated complications, while simultaneously reducing the percentage of women with inadequate weight gain. Potential unintended consequences, such as excess weight gain, should be considered when implementing smoking cessation interventions for pregnant women. Such interventions could, for example, incorporate weight management programs for at-risk women.

The evidence related to cessation and reduced fertility in men and women remains mixed and inconclusive, and our understanding of the mechanism(s) underlying these effects is limited, especially for women. Further research is needed to determine whether and when in the life course cessation of smoking needs to occur to benefit female and male fertility. Such evidence is needed so that the appropriate information can be communicated to patients and providers so that interventions can be tailored accordingly.

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