

Chapter 6

Cancer

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Sections of this chapter on the health consequences of smoking are accompanied by evidence tables detailing the studies that were used to evaluate the evidence to assess causality. A supplement to this report is provided that contains these tables. The tables included in the supplement are indicated with an “S” where they are called out in the text.

Introduction

The signature finding of the landmark 1964 Surgeon General’s report, *Smoking and Health*, was the conclusion that cigarette smoking was a cause of lung cancer in men (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). At that time, cancer was a highly feared disease with limited therapeutic options (Mukherjee 2010). Surgery and radiation therapy were essentially the only treatment options, as chemotherapy was in its infancy. The efficacy of chemotherapy for childhood acute lymphoblastic leukemia and for testicular cancer had not yet been established (Proctor 1995). Chemoprevention, as now used for breast cancer, for example, had not been implemented. Screening was employed for only one disease, cervical cancer, using the Papanicolaou (Pap) smear. The first trial of mammographic screening for breast cancer, the Health Insurance Plan (HIP) study, had just been launched (Mukherjee 2010). Many of the most critical advances in mechanistic understanding that are relevant to prevention and treatment today had yet to arrive (Table 6.1) (DeVita and Rosenberg 2012).

From the perspective of 2014, the understanding 50 years ago of the pathogenesis and etiology of cancer was also quite limited (Figure 6.1) (DeVita and Rosenberg 2012). Radiation was a long-established cause of multiple types of cancer; the increased risk of lung cancer in radon-exposed uranium miners was established; and follow-up of the atomic bomb survivors had documented their increased risk of acute leukemia. Clinical experience and epidemiologic studies were documenting links between occupational exposures, including asbestos and nickel oxides, and cancer. The wave of epidemiologic studies that focused on lifestyle and risk of cancer was just starting, and relatively little attention was given to viruses and bacteria as causes of cancer.

The process of carcinogenesis was commonly understood as prolonged and involving multiple stages, leading to uncontrolled cell replication (Armitage and Doll 1954; Shimkin 1977). The 1964 Surgeon General report’s discussion of carcinogenesis referred to “...a slow multi-stage process” (p. 142) and pointed out that some chemicals are

“initiators,” causing permanent changes in cells, while others are “promoters” of the carcinogenic process. The structure of DNA and the genetic code were identified, but research on DNA, mutations, and cancer was just starting (Table 6.1). Of course, many processes now considered to be critical in carcinogenesis (e.g., those involving oncogenes, tumor suppressor genes, and epigenetics) had not yet been discovered.

Figures 4.3 and 4.4 document trends in cancer mortality among men and women for the period 1930–2010 (American Cancer Society [ACS] 2013). However, mortality does not capture the full picture of cancer occurrence, since it matches incidence (i.e., the occurrence of new cases) for only those malignancies for which survival is very poor. For lung cancer, given a 5-year survival rate of around 15%, incidence and death rates are close. In 1964, lung cancer was the leading cause of cancer deaths in men, having passed colorectal cancer about a decade previously. Death rates for stomach cancer had declined steadily in men and women, as had the uterine (corpus and cervix) cancer mortality rate for women. The lung cancer mortality rate in 1964 for women was just starting its upward trajectory. Figure 4.3 charts the continuing course of lung cancer death rates, showing an eventual plateau and decline in men. Figure 4.4 shows a long upward course and then the beginning of a decline in women.

Overall, cancer survival has also improved in the United States. In 1953, relative 5-year survival for people with cancer was only 35% (DeVita and Rosenberg 2012). By 1977, the figure was 49% and the most recent data from the National Cancer Institute’s (NCI’s) Surveillance, Epidemiology, and End Results (SEER) Program for cases diagnosed between 2003–2009 and followed through 2010 was 68% (NCI 2013).

Since 1973, the incidence of cancer has been tracked in some states and metropolitan areas through the SEER Program. Figures 6.2 and 6.3 show trends for age-adjusted incidence of cigarette-caused cancers across the span covered by the SEER data among men and women. Among men, incidence rates of lung, colorectal, oropharyngeal,

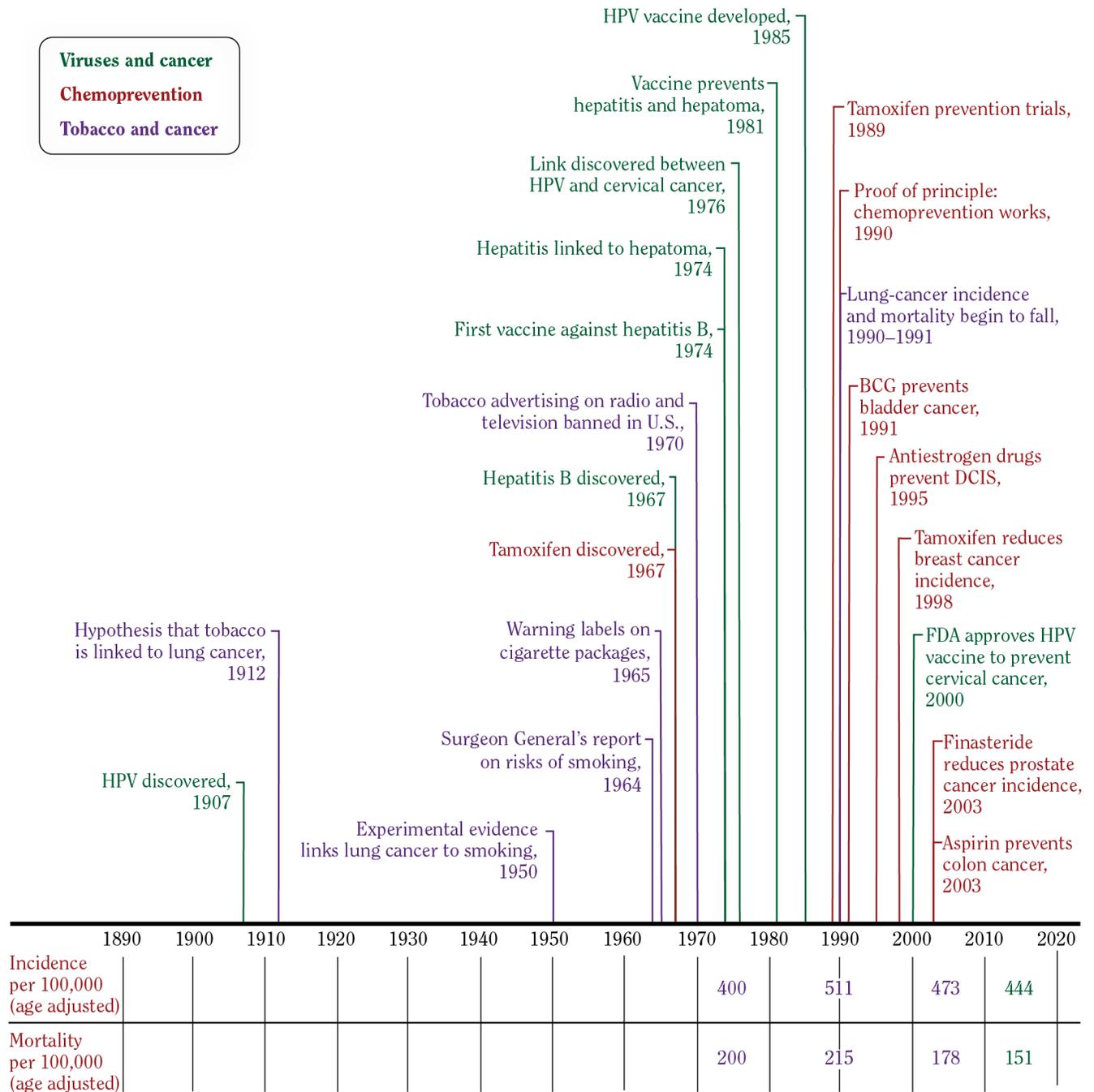
Table 6.1 Singular discoveries and major events in the cancer field and changing relative survival rates for persons with cancer in the United States, 1863–2006

Year	Discovery or event	Relative 5-year survival rate
1863	Cellular origin of cancer (Virchow)	
1889	Seed-and-soil hypothesis (Paget)	
1914	Chromosomal mutations in cancer (Boveri)	
1937	Founding of the National Cancer Institute	
1944	Transmission of cellular information by DNA (Avery)	
1950	Availability of cancer drugs through CCNSC	
1953	Report on structure of DNA	35%
1961	Breaking of the genetic code	
1970	Reverse transcriptase	
1971	Restriction enzymes Passage of <i>National Cancer Act of 1971</i>	
1975	Hybridomas and monoclonal antibodies Tracking of cancer statistics by SEER Program	50%
1976	Cellular origin of retroviral oncogenes	
1979	Epidermal growth factor and receptor	
1981	Suppression of tumor growth by <i>P53</i>	
1982	Discovery of <i>RAS</i> oncogenes	
1984	G proteins and cell signaling	
1986	Retinoblastoma gene	
1990	First decrease in cancer incidence and mortality	
1991	Association between mutation in <i>APC</i> gene and colorectal cancer	
1994	Genetic cancer syndromes Association between <i>BRCA1</i> and breast cancer	
2000	Sequencing of the human genome	
2002	Epigenetics in cancer Micro-RNAs in cancer	
2005	First decrease in total number of deaths from cancer	68%
2006	Tumor stromal interaction	

Source: Adapted from DeVita and Rosenberg 2012 using data from Chang et al. 1982. Reprinted with permission from Massachusetts Medical Society, © 2012.

Note: CCNSC = Cancer Chemotherapy National Service Center; SEER = Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.

Figure 6.1 Timeline of pivotal events in cancer prevention



Source: DeVita and Rosenberg 2012. Reprinted with permission from Massachusetts Medical Society, © 2012.

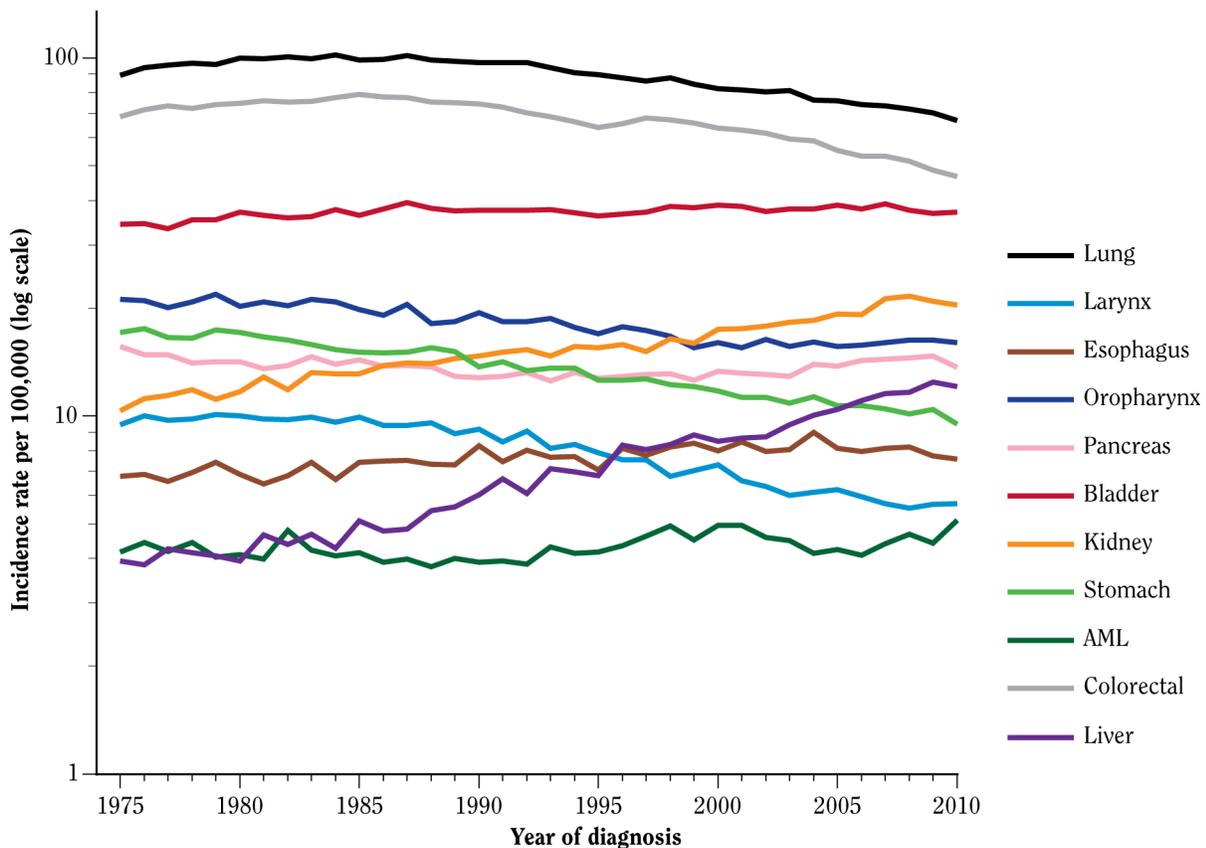
Notes: **BCG** = bacille Calmette-Guérin; **DCIS** = ductal carcinoma in situ; **FDA** = U.S. Food and Drug Administration; **HPV** = human papilloma virus.

stomach, and laryngeal cancers have declined over time, but rates for kidney and liver cancers continue to rise. The trend is similar among women, with the exception of lung cancer for which incidence rates increased in the two decades since 1975, and reached a plateau since the mid-1990s, before declining in 2007 (Howlader et al. 2013). In addition to the SEER areas, the rest of the nation and the District of Columbia are covered by the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Prevention (CDC). The *Annual Report to the Nation on the Status of Cancer*, a collaborative publication by the ACS, the North American Association of Central Cancer Registries, CDC, and NCI, provides an

ongoing assessment of progress in cancer control. The most recent report reveals a decline in the incidence of lung cancer for both men and women in the first decade of the twenty-first century (Jemal et al. 2013). For men, the rate declined by 2.0% annually during this decade, while the annual decline was 0.2% for women.

This chapter reviews the evidence on smoking and cancer for malignancies for which the evidence was previously found to be inadequate or was insufficient to reach a causal conclusion. Specifically, four cancer sites are covered—breast, colon and rectum, liver, and prostate—and also the changing cigarette and risk for lung cancer over time. The chapter also covers the rela-

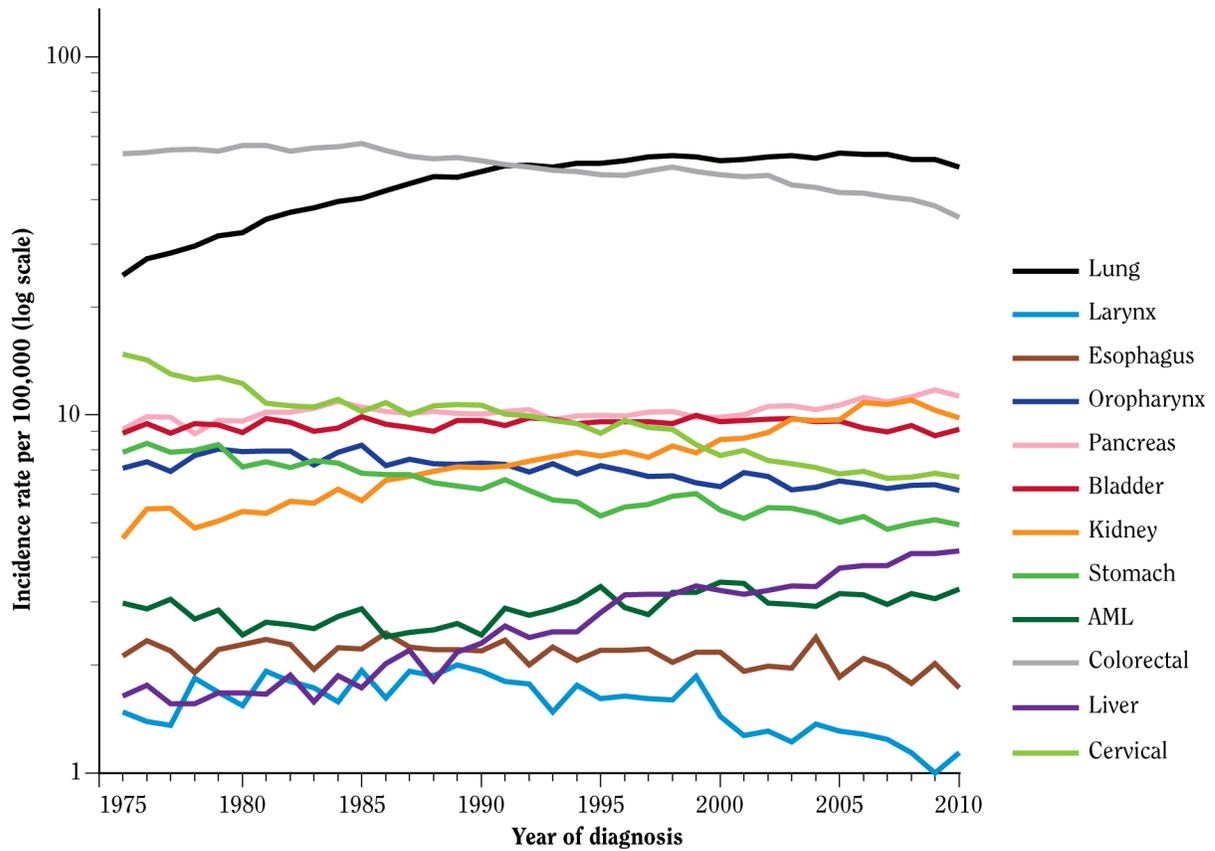
Figure 6.2 Surveillance, Epidemiology, and End Results (SEER) age-adjusted incidence, selected sites, males, 1975–2010



Source: Howlader et al. 2013.

Note: The data are for nine SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25-1130). **AML** = acute myeloid leukemia.

Figure 6.3 Surveillance, Epidemiology, and End Results (SEER) age-adjusted incidence, selected sites, females, 1975–2010



Source: Howlader et al. 2013.

Note: The data are for nine SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25-1130). **AML** = acute myeloid leukemia.

tionship between smoking and the outcome of cancer, a topic not previously addressed in the reports of the Surgeon General on smoking and health. Previous reviews related to cancer were included in the 2004 Surgeon General’s report on active smoking (U.S. Department of Health and Human Services [USDHHS] 2004) and in the 2006 report on exposure to secondhand smoke (USDHHS

2006). Figure 1.1A shows those malignancies for which the Surgeon General’s reports classified the relationship with smoking as causal. The chapter begins with an overview of the mechanisms by which smoking causes cancer, based on the indepth coverage of this topic in the 2010 Surgeon General’s report *How Tobacco Smoke Causes Disease* (USDHHS 2010).

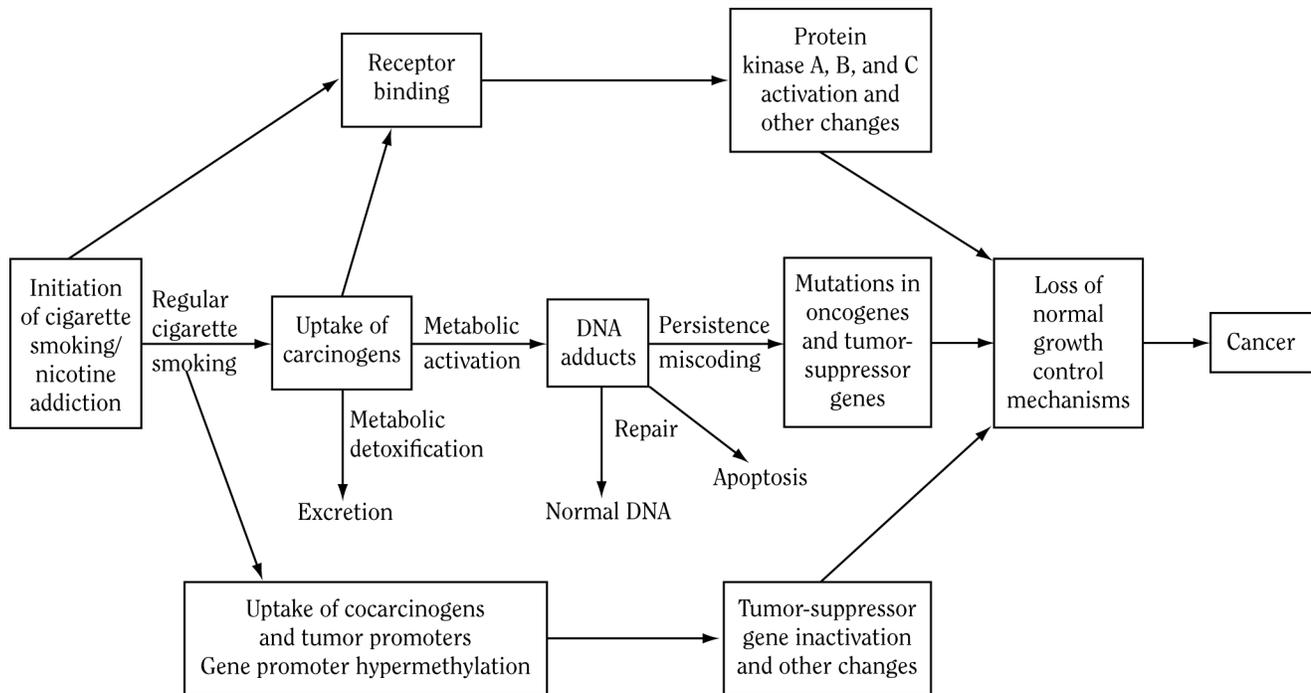
Mechanisms of Cancer Induction by Tobacco Smoke

Classic studies demonstrating the covalent binding of carcinogens, or their reactive electrophilic metabolites, to cellular macromolecules (including DNA) were published at about the same time as the 1964 Surgeon General's report on smoking and health (USDHEW 1964; Miller and Miller 1976). Building on these seminal observations, many researchers explored this mechanistic concept in detail and confirmed it for different classes of chemical carcinogens; that line of research continues even today (Searle 1984; Loebe and Harris 2008; Penning 2011). Tobacco smoke, with its multiple carcinogens, recapitulates the classic mechanisms established in these studies. The general concept of exposure to carcinogens, metabolism to reactive intermediates, and DNA damage leading to mutations in critical genes has been established as one major mechanism by which tobacco smoke causes cancer. This topic was discussed in some detail in Chapter 5 of the 2010 Surgeon General's report. A mechanistic framework encompassing these steps and related phenomena was presented in that report and in related publications, and

it is reproduced here as Figure 6.4 (Hecht 1999, 2012a). This section will present a brief overview of the relevant steps in Figure 6.4 and a more detailed discussion of some recent findings pertinent to this overall mechanism.

People begin to smoke cigarettes at a relatively young age, typically have difficulty stopping, and may continue to smoke for decades. Nicotine is addictive, but is not a direct chemical carcinogen (see Chapter 5, "Nicotine") (Maier et al. 2011; Murphy et al. 2011). However, by creating and sustaining addiction, it leads to the prolonged exposure to tobacco smoke that increases cancer risk for smokers. When smokers inhale smoke, each cigarette puff delivers a mixture of carcinogens and toxicants. Tobacco smoke contains more than 7,000 chemicals, and at least 69 of these can cause cancer (USDHHS 2010). These include polycyclic aromatic hydrocarbons (PAHs); tobacco-specific nitrosamines; aromatic amines; and volatile carcinogens such as formaldehyde, acetaldehyde, 1,3-butadiene, and benzene (as well as various metals).

Figure 6.4 Pathway for causation of cancer by carcinogens in tobacco smoke



Source: Modified from U.S. Department of Health and Human Services 2010.

Most constituents of cigarette smoke, including the carcinogens, are compounds foreign to the human body and, consequently, are acted upon by metabolizing enzymes designed to detoxify them. These enzymes, including cytochrome P-450, glutathione *S*-transferases, and UDP-glucuronosyl transferases and sulfotransferases, catalyze the conversion of these foreign compounds to more water-soluble products that can be easily excreted from the body. But during this process, certain reactive compounds may be formed as intermediates. Examples of these reactive intermediates include electrophilic carbocations or epoxides that can bind covalently to nucleophilic sites in DNA, including the nitrogen and oxygen atoms of DNA nucleobases. These binding products are known as DNA adducts and are critical in carcinogenesis if they are not fixed by DNA repair enzymes. Persons with rare syndromes in which DNA repair is deficient, such as *Xeroderma pigmentosum*, are highly prone to cancer development; people with this syndrome develop skin cancer because of the multiple types of DNA damage that result from exposure to sunlight (Weinberg 2007).

There is convincing evidence for the presence of DNA adducts in the lungs and other tissues of smokers in amounts generally higher than those found in nonsmokers. While many of these adducts remain unidentified, a number of studies have characterized specific carcinogen-DNA adducts in the tissues of smokers (Phillips and Venitt 2012).

If the DNA adducts produced by tobacco smoke carcinogens and their metabolites evade repair systems and remain, they can cause miscoding during DNA replication when bypass DNA polymerase enzymes direct the placement of an incorrect nucleobase opposite the adduct (USDHHS 2010). This can result in a permanent mutation in the DNA sequence. If this mutation occurs in an important section of a cellular oncogene such as *KRAS*, or in a tumor suppressor gene such as *TP53*, the result can be an alteration of the normal growth control mechanisms, leading to uncontrolled proliferation, further mutations, and cancer. Multiple studies, using state-of-the-art methods, have shown that thousands of mutations are present in the DNA of lung tumors from smokers, including in critical growth regulatory genes, most frequently *KRAS* and *TP53*. These genes are discussed in more detail below (Greenman et al. 2007; Ding et al. 2008a; Lee et al. 2010c; Pleasance et al. 2010).

Some constituents of tobacco smoke or their metabolites may bind directly to cellular receptors, leading to activation of protein kinases, growth receptors, and other pathways, which can contribute to carcinogenesis (Chen et al. 2011b). Cigarette smoke contains substances that

can induce inflammation resulting in enhanced pneumocyte proliferation, activation of nuclear factor-kappa B (NF- κ B), and tumor promotion (Takahashi et al. 2010). Cigarette smoke also has cocarcinogens which, while not carcinogenic themselves, enhance the smoke's carcinogenic effects. Further, cigarette smoke induces oxidative damage and gene promoter methylation, processes that also likely contribute to cancer development.

In the last few years, there have been some developments that were not fully covered in the 2010 Surgeon General's report, but are pertinent to a fuller understanding of the mechanisms of carcinogenesis by cigarette smoke. They are discussed briefly here.

Addiction to nicotine results from its binding to nicotinic acetylcholine receptors (nAChRs). An association between common variants in the *CHRNA5-CHRNA3-CHRNA4* nAChRs subunit gene cluster on chromosome 15q25 and the risk of lung cancer was reported in three genome-wide association studies (Amos et al. 2008; Hung et al. 2008; Thorgeirsson et al. 2008). These genes are strongly associated with nicotine dependence (Saccone et al. 2007), and multiple studies have confirmed and amplified these observations (Saccone et al. 2009, 2010; Timofeeva et al. 2011; Wang et al. 2011; Ware et al. 2011; Wassenaar et al. 2011). These results are likely due to changes in smoking behavior causing an increased uptake of nicotine as well as a greater presence of lung carcinogens, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), in carriers of the gene variants described above (Le Marchand et al. 2008). The increased uptake of nicotine, which was confirmed by measurement of its metabolite cotinine in a similar study based on the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, is a surrogate for the uptake of carcinogens and toxicants in cigarette smoke (Timofeeva et al. 2011; Yuan et al. 2011a, 2012). Thus, carriers of the gene variants smoke their cigarettes more intensely and are exposed to higher levels of NNK and other carcinogens in smoke, thereby increasing their risk of lung cancer.

Modern DNA-sequencing methods allow scientists to carry out detailed investigations of mutations in human cancers. Because there are multiple carcinogens in cigarette smoke and multiple DNA adducts in the lungs of smokers, one would expect to find many mutations within critical genes in the lung tumors from smokers. Sequencing studies are consistent with this expectation. For example, when Greenman and colleagues (2007) investigated mutations in the coding exons of more than 500 protein kinase genes, they found that lung cancers were among those with the most somatic mutations (4.21 per megabase). The authors attributed this finding to

recurrent exposure to exogenous mutagens (Greenman et al. 2007). Another investigation sequenced 188 primary lung adenocarcinomas; altogether, 247 megabases of tumor DNA sequence were analyzed and 1,013 nonsynonymous somatic mutations in 163 of the 188 tumors were identified, including 915 point mutations, 12 dinucleotide mutations, 29 insertions, and 57 deletions (Ding et al. 2008a). Twenty-six significantly mutated genes were identified, including oncogenes and tumor suppressor genes commonly found to be mutated in lung cancer, such as *TP53*, *KRAS*, *CDKN2A*, *STK11*, and others. Mutations were most common in *TP53* and *KRAS*.

More recently, a report on complete exome and genome sequences of 183 lung adenocarcinomas revealed a mean exonic somatic mutation rate of 12.0 events per megabase (Imielinski et al. 2012). Analysis of nucleotide context-specific mutation signatures grouped the sample set into distinct clusters that correlated with smoking history and alterations of reported lung adenocarcinoma genes. Elsewhere, Pleasance and colleagues (2010) sequenced a small-cell lung cancer cell line; these investigators identified 22,190 somatic substitutions, including 134 in coding exons. They found that *G*→*T* transversions were the most common (34%), followed by *G*→*A* transitions (21%) and *A*→*G* transitions (19%). These results are similar to data that have been obtained by analysis of the *TP53* gene, which is discussed later in this overview. Elsewhere, a case report focused on a non-small-cell lung cancer (NSCLC) from a 51-year-old patient who had smoked 25 cigarettes per day for 15 years prior to excision of the tumor, which yielded a poorly differentiated sample with 95% tumor content, most likely an adenocarcinoma (Lee et al. 2010c). In this patient, single nucleotide variants were common, mostly at *G*→*C* base pairs, frequently *G*→*T* transversions; these were statistically distinct from germline mutations. More than 50,000 single nucleotide variants were observed, approximately 17.7 mutations per megabase. At least eight genes in the EGFR-RAS-RAF-MEK-ERK pathway were either mutated or amplified.

In another investigation, whole-exome sequencing and gene copy number analyses were used to study 32 primary head and neck squamous cell carcinomas (Agrawal et al. 2011). Tumors from patients with a history of tobacco use had more mutations than did tumors from patients who did not use tobacco, and tumors that were negative for human papilloma virus (HPV) had more mutations than did HPV-positive tumors. Six of the genes that were mutated in multiple tumors were assessed in up to 88 additional head and neck squamous cell carcinomas. In addition to previously described mutations in

TP53, *CDKN2A*, *PIK3CA*, and *HRAS*, new frequent mutations were found in *FBXW7* and *NOTCH1*. In all, 11 of the 28 mutations (39%) identified in *NOTCH1* were predicted to truncate the gene product, suggesting that *NOTCH1* may function as a tumor suppressor gene rather than as an oncogene in this tumor type. Moreover, a similar study of 78 additional tumors reported that 30% of the cases harbored mutations in genes that regulate squamous differentiation (including *NOTCH1*, *IRF6*, and *TP63*), implicating such dysregulation as a major driver of carcinogenesis in head and neck squamous cell carcinoma (Stransky et al. 2011).

The results of these studies are consistent with those reported in the 2010 Surgeon General's report and with information found in the COSMIC (Catalogue of Somatic Mutations in Cancer) database (Wellcome Trust and Cancer Research Institute 2012), which stores and displays somatic mutations in genes associated with cancer, such as *TP53* and *KRAS*. Collectively, the available results of late-generation sequencing studies, as well as the extensive databases on *TP53* and *KRAS* mutations, are completely consistent with the induction of multiple mutations in critical growth control genes by metabolically activated carcinogens of cigarette smoke, although other processes downstream from exposure to carcinogens could also contribute.

Epigenetic changes, defined as nonsequence DNA changes, are also an integral part of cancer progression. Gene promoter hypermethylation is an epigenetic change, involving extensive methylation at the 5-position of C in CpG islands within the promoter region, and, often, extending into exon 1 of regulatory genes (Jones and Baylin 2002). In lung cancer, more than 750 genes are inactivated by gene promoter hypermethylation, and new genes are still being identified through genomewide screening approaches (Selamat 2012). The end result of this process can be the loss of gene transcription and, therefore, the silencing of gene function. Comparison of DNA methylation profiles between lung adenocarcinomas of current and never smokers, using a genomewide platform, showed only modest differences between the groups, and it identified only *LGALS4* as significantly hypermethylated and downregulated in smokers (Selamat et al. 2012). Analysis of the DNA methylation data identified two tumor subgroups, one of which showed increased DNA methylation and was significantly associated with *KRAS* mutation and, to a lesser extent, with smoking. Promoter methylation of several genes, including *PI6*, occurs early in tumor formation. One study of head and neck cancer found that *PI6* methylation was significantly and positively associated with pack-years¹ of smoking and was an independent risk factor for overall survival, being

¹Pack-years = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

significantly associated with shorter survival in patients with early resectable adenocarcinomas (Ai et al. 2003). In that study, *PI6* promoter hypermethylation also correlated significantly with a history of alcohol consumption or tobacco use in head and neck cancer. Other genes, such as *BRMS1* and *RASSF1A*, may be more frequently methylated in various tumor types from smokers. In a study by Tessema and colleagues (2009), the frequency of methylation of *TNFRSF10C*, *BHLHB5*, and *BOLL* was significantly higher in adenocarcinomas from never smokers than in those from smokers. Methylation of genes, such as *MGMT* and *AGT* promoter hypermethylation, may increase G→A transition mutations at CpG sites within the *TP53* gene in NSCLC.

These data in aggregate support the pathways illustrated in Figure 6.4. The contribution of specific tobacco smoke carcinogens to lung cancer (and also to esophageal cancer) has been investigated in several nested case-control studies as well. In these studies, the carcinogens or their metabolites were quantified in stored urine samples that were collected from smokers years or decades before cancer developed. For example, using frozen urine samples collected during the 1980s from more than 18,000 smokers in Shanghai, China, scientists have found that specific metabolite levels were associated with an increased risk of lung or esophageal cancer, even after correction for the number of years of smoking and number of cigarettes smoked per day (Yuan et al. 2009, 2011a,b). Thus, significantly elevated risks for lung cancer were associated with increased levels of the NNK metabolites' total NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides] and the PAH metabolite phenanthrene tetraol. The strongest elevated risk was for esophageal cancer in individuals with the highest levels of the tobacco-specific carcinogen *N*'-nitrosonornicotine and its glucuronides in their urine.

This carcinogen induces a high incidence of esophageal tumors in rats (Yuan et al. 2009, 2011a,b).

Smokers experience proinflammatory changes in their lungs. Inflammation is intimately associated with activation of NF- κ B and tumor promotion (Malkinson 2005; Smith et al. 2006; Lee et al. 2008), and many studies in laboratory animals demonstrate that anti-inflammatory agents can decrease tobacco carcinogen-induced lung tumorigenesis (Hecht et al. 2009). In addition, chronic obstructive pulmonary disease, particularly emphysema, is an independent risk factor for lung cancer in smokers. This association further implicates a strong role for inflammation in lung cancer (Turner et al. 2007). In one study, the tumor-promoting activity of cigarette smoke was examined in mouse models of lung tumorigenesis (Takahashi et al. 2010); here, exposure to smoke after treatment of A/J mice with NNK increased the multiplicity of lung tumors. Similar results were obtained in *KRAS*^{L42} mice harboring a mutation in *KRAS* codon 12 identical to that caused by NNK. I κ B kinase β (IKK β) was required for NF- κ B activation and played a critical role in tumor promotion in this system, most likely through the induction of inflammation and related phenomena (Takahashi et al. 2010). These studies amplify and extend earlier observations demonstrating the tumor-promoting activity of cigarette smoke.

Summary

Understanding of the mechanisms by which smoking causes cancer continues to advance. An overall framework for the causation of cancer by tobacco smoking was set out in the 2010 Surgeon General's report. The utility of that framework is supported by new experimental findings as well as by ongoing studies of smokers in the population.

Changing Cigarettes and Risk for Lung Cancer Over Time

Cigarette smoking is the predominant cause of lung cancer in the United States, and lung cancer is the country's leading cause of cancer death (USDHHS 2004). Cigarette smoke, which contains multiple carcinogens (Hoffmann and Hoffmann 1997; IARC 2004; USDHHS 2004; Rodgman and Perfetti 2009), is composed of gases and particles with a distribution of size that result in substantial deposition in the lung when the smoke is inhaled (Stratton et al. 2001; Gower and Hammond 2007). The composition of tobacco smoke varies with cigarette

type (e.g., filtered or unfiltered) and across brands of the same type (IARC 2004; Burns et al. 2008; World Health Organization [WHO] 2008b). Over past decades, multiple substantive changes in the design and composition of cigarettes have altered the chemistry of tobacco smoke raising the question as to whether lung cancer risks have changed in response (Hoffmann and Hoffmann 1997; Rodgman and Perfetti 2009). This section reviews evidence relevant to this question.

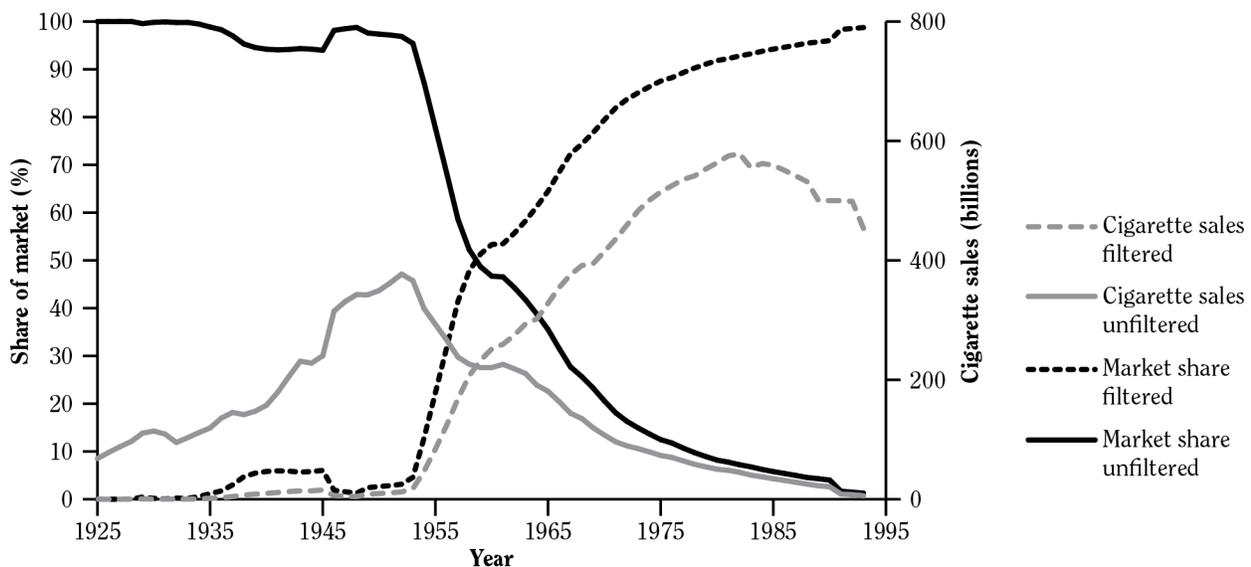
This section focuses on lung cancer because it is the cancer most related to cigarette smoking (USDHHS 2004). Substantial data are available, both over time and from many countries, on the occurrence of lung cancer, both generally and by histologic type. The topic of lung cancer in relation to smoking has been addressed in depth in several past reports of the Surgeon General. These reports have focused on levels of machine-measured tar and nicotine in relation to risk and have considered whether changes in design and characteristics that have lowered the tar yield of cigarettes have also reduced the risk of diseases caused by smoking (USDHHS 1981, 2004). The 2004 Surgeon General's report on the health consequences of smoking concluded that no substantive reduction in the risk of disease was associated with using cigarettes with low levels of tar, as measured by machine. This and earlier reports clearly document that machine-measured tar yields have little relationship to the doses actually received by smokers because of the phenomenon of compensation. This section focuses mainly on whether the changes in the design and composition of cigarettes over time that paralleled the reduction in tar yields (by machine measurement) may have altered—and possibly even increased—the risk of lung cancer associated with cigarette smoking. The analysis is limited to cigarette design issues and does not consider other issues, such

as changing nicotine yields and the marketing of various types of cigarettes. This section does not explore the implications of these changes for diseases other than lung cancer.

Changes in Cigarettes Over the Past Several Decades

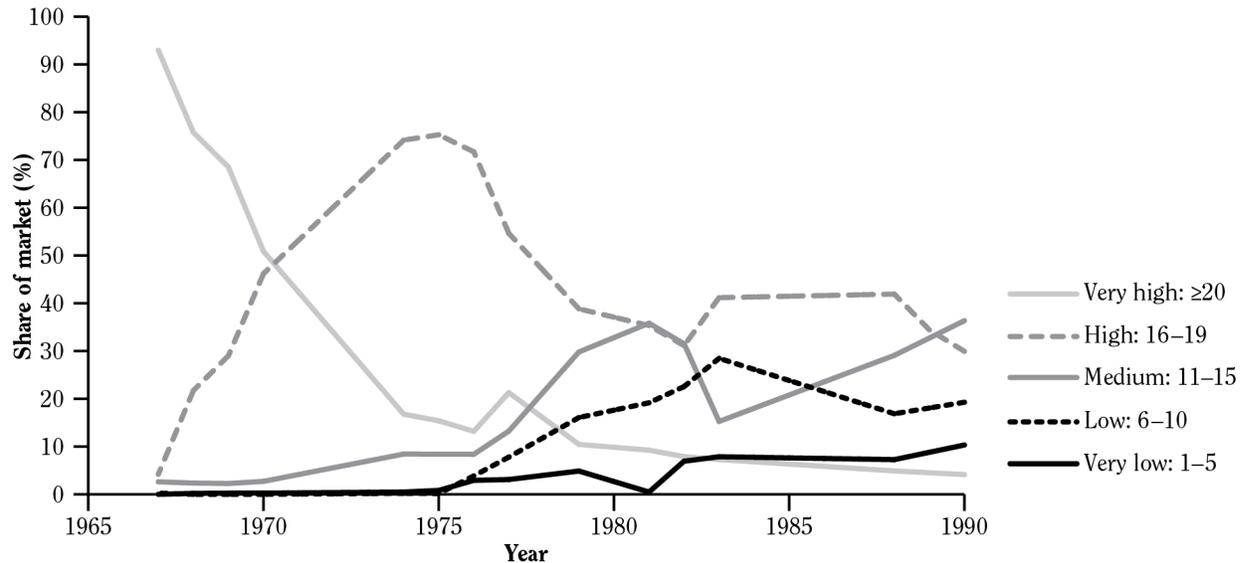
Since the 1950s, cigarettes have undergone changes in their design and composition (Hoffmann and Hoffmann 1997; NCI 2001). The most prominent changes have been the addition of filters and the use of ventilation holes in the filters to lower machine-measured tar and nicotine yields. Figure 6.5 shows the rapid rise in the use of filtered cigarettes that followed the heavy marketing of such cigarettes in the mid-1950s. The marketing effort promised a lower risk product to smokers who had become concerned about the disease risks of smoking (Brandt 2007). This shift to filters continued and today almost all manufactured cigarettes currently consumed in the United States are filtered (Hoffmann and Hoffmann 1997; NCI 2001). Figure 6.6 shows the move to cigarettes with lower tar yields, beginning with a shift from brands with more than 20 milligrams (mg) of machine-measured tar

Figure 6.5 Market share and total annual cigarette sales of filtered and unfiltered cigarettes in the United States, 1925–1993



Source: National Cancer Institute 2001; data from Maxwell 1994.

Figure 6.6 Market share of total cigarettes sold per year, by tar yield (milligrams [mgs] of tar by Federal Trade Commission method), United States, 1967–1990



Source: National Cancer Institute 2001; data from Maxwell 1994.

Note: Tar levels for given years are derived from Federal Trade Commission reports (for years 1967–1990). Sales data by brand are from Maxwell (1994). Brand-specific market shares are summed by tar level of the brand in the given year to generate the market share for cigarettes with given tar yields.

to lower tar-yielding brands in the late 1960s and early 1970s (NCI 2001). By 1990, about two-thirds of cigarettes sold had either medium (11–15 mg), low (6–10 mg), or very low (1–5 mg) yields of tar. The principal mechanism underlying the lower yields of machine-measured tar was the increase in the number and the size of ventilation holes in the filter, thereby diluting the smoke entering the machine (Hoffmann and Hoffmann 1997; NCI 2001). Although these changes reduced tar delivery as measured by the U.S. Federal Trade Commission's (FTC's) protocol, which did not reflect how smokers actually smoke; they did not reduce the risks of disease and premature mortality in smokers (NCI 2001; USDHHS 2004).

Epidemiologic evaluations of risk and assessments of smoke chemistry during the decades in which these substantial changes occurred tended to treat all cigarettes as if they were equivalent, both over time and across brands. The exception was that these evaluations did consider the machine-measured tar and nicotine yields and whether they were filtered. However, the design and composition of cigarettes changed substantially in other ways, even as they were continuously redesigned to deliver ever lower machine-measured yields of substances. Unfortunately,

researchers in the past did not have access to information about the nature and extent of these and other changes in cigarettes because they were handled as trade secrets and, therefore, not disclosed by the industry.

Changes in Design, Curing, and Composition

Although smokers may perceive cigarettes as very simple devices: chopped-up tobacco rolled in paper, perhaps with a filter attached to the end, the reality, however, is that cigarettes are highly engineered products (Hoffmann and Hoffmann 1997; Rodgman and Perfetti 2009; Proctor 2011). The design features of cigarettes can have significant effects on the composition of the tobacco smoke and perhaps its toxicity. Over time, changes to cigarettes have become progressively more extensive and more complex, further complicating the efforts of researchers to understand their health implications (Hoffmann and Hoffmann 1997; NCI 2001; O'Connor et al. 2008; O'Connor and Hurley 2008; WHO 2008b). Many factors can influence the chemistry of tobacco smoke: (1) the geographic location where the tobacco is grown (which can alter the heavy metal content of smoke, for example) (IARC 2004,

2007); (2) agricultural practices (which can influence levels of nitrates and pesticides, but also polonium and heavy metal content as well) (Hoffmann and Hoffmann 1997; Rodgman and Perfetti 2009); (3) how the tobacco is cured and processed (which can influence tobacco-specific nitrosamine levels and other factors) (Hoffmann and Hoffmann 1997; NCI 2001; Peele et al. 2001; O'Connor et al. 2008; O'Connor and Hurley 2008); (4) the blend of tobacco used; (5) the use of reconstituted tobacco sheet and puffed tobacco (tobacco expanded through an industrial process) (Hoffmann and Hoffmann 1997; IARC 2004, 2007; O'Connor et al. 2008; O'Connor and Hurley 2008; Rodgman and Perfetti 2009); (6) the engineering characteristics of the manufacturing process (Hoffmann and Hoffmann 1997; O'Connor et al. 2008; O'Connor and Hurley 2008; Rodgman and Perfetti 2009); (7) the additives used in tobacco; and (8) the pattern of puffing the smoker uses to generate the smoke (which can alter the quantity of smoke generated and the relative composition of its constituents) (WHO 2007, 2008b; Burns et al. 2008).

Cigarettes in Australia, Canada, and the United Kingdom are made primarily of flue-cured tobacco, but most brands sold in the United States use a blend of air-cured tobaccos (Hoffmann and Hoffmann 1997; IARC 2004; WHO 2008b; Rodgman and Perfetti 2009). In addition, substantial amounts of reconstituted tobacco sheet and puffed tobacco are added to the blend. The soil in which the tobacco is grown, the agricultural practices used, and the methods of curing and processing the tobacco also differ across brands and have changed over time (Hoffmann and Hoffmann 1997; Peele et al. 2001; IARC 2004; Rodgman and Perfetti 2009). Flavoring agents; processing aids, such as humectants; chemicals intended to alter the pH of the smoke; and other agents are added to tobacco as part of the manufacturing process.

Approaches used to alter the processes of generating smoke may involve the cut size of the reconstituted tobacco sheet, filter ventilation, the density of the tobacco in the rod, the composition and design of the filter material, the porosity of the cigarette paper, and other factors (Hoffmann and Hoffmann 1997; O'Connor et al. 2008; O'Connor and Hurley 2008; Rodgman and Perfetti 2009). The pattern the smoker uses to puff the cigarette is superimposed on all of its intrinsic characteristics. This pattern varies among smokers and can change with different types of cigarettes smoked by the same smoker; it can also change systematically across smokers in response to certain design features, most notably filters and ventilation (NCI 2001; WHO 2008b). Rodgman and Perfetti (2009), O'Connor and colleagues (2008), and O'Connor and Hurley (2008) have reviewed the impact of many of these factors on the composition of tobacco smoke, but a detailed

review of the extensive literature describing the effect of isolated changes on smoke composition is beyond the scope of this section.

Beyond the data held by the manufacturers, the details on differences in the design and composition of cigarettes across U.S. brands are not available in a systematic form. Complete and representative information is also not available over time on the composition of smoke generated by individual brands or on the changes in manufacturing practices for different brands. Longitudinal data on brands marketed in the United States are limited to data—using FTC's protocol—on machine-measured yields of the tar, nicotine, and carbon monoxide produced. Without this information, the research and public health communities have been unable to fully assess the potential effects of changes in the design and composition of cigarettes on smokers' exposures over time to toxicants in cigarette smoke. Nevertheless, the limited data that exist allow for some assessment of likely changes in smoke toxicity following changes that have been made in cigarettes.

Differences Across Brands in Toxicant Yields

Of the 7,000 or more constituents in tobacco and tobacco smoke, 69 have been identified as carcinogens (USDHHS 2010). The complexity and expense of measuring multiple constituents for all the different brands under multiple sets of machine parameters have led tobacco industry scientists to suggest that constituent yields can be benchmarked and reliably predicted from machine-measured tar yields (Counts et al. 2004, 2005, 2006; Morton and Laffoon 2008). This concept is based on the assumed relationship between the total mass of smoke and its nicotine content, as measured by a smoking machine. However, the mass of smoke generated by a smoking machine using any fixed protocol bears little relationship to the amount of smoke inhaled by a smoker or to the differences between brands in smoke exposure (Jarvis et al. 2001; NCI 2001). A more appropriate method for examining the variation in constituent yields across brands is to examine these yields after they have been normalized per mg of tar or per mg of nicotine to characterize the variation that might be experienced for a given level of nicotine intake.

Nicotine is the principal addictive constituent sought by the smoker and the ratio of tar to nicotine is relatively constant across brands. When the Massachusetts Benchmark Study data on yields for a 1999 sample of U.S. brands of cigarettes are normalized per mg of tar or per mg of nicotine, the ability of tar yields to predict the variation in yields of other constituents is poor (Harris 2001, 2004). In fact, the normalized yields of several

constituents are higher for cigarettes with low machine-measured tar yields than for those whose machine-measured tar yields are high (Harris 2004).

Table 6.2 presents the variability in the yields of a variety of constituents across brands, normalized per mg of tar or per mg of nicotine, from the Massachusetts Benchmark Study sample of U.S. cigarettes in 1999. In this table, the coefficient of variation across brands (which represents the standard deviation of the measurements across brands normalized to the mean value of that constituent for all brands) is divided by the mean standard deviation of replicate measurements for that constituent. This formulation expresses the variation of constituents across brands in relation to the precision with which the constituent can be measured. Table 6.2 demonstrates that for many of the toxicants measured, the variation in constituents across brands, normalized per mg of tar or per mg of nicotine, is many times higher than can be explained by the variability of the measurement. Clearly, at least in terms of constituent yields from machine-generated cigarette smoke, smoke from all cigarettes is not uniform in composition. This variability is likely not limited to 1999, when the cigarettes were sampled, or to have remained constant over time. Furthermore, normalized constituent yields in Canadian and Australian cigarette brands and a sample of international blended cigarette brands manufactured by Philip Morris International have demonstrated similar variability (WHO 2008b). In addition, when biomarkers of exposure to specific toxicants are assessed, the data show considerable variability in their levels among smokers, particularly in heavy smokers (Joseph et al. 2005); this finding is consistent with variation in exposure due to differences in smoke composition across brands and to inherent variability among smokers.

Changes in Tobacco-Specific Nitrosamine and Benzo[a]pyrene Levels Over Time

Because only limited longitudinal data are available for toxicant yields, changes in these yields over time are difficult to characterize accurately for all brands. However, for one major U.S. brand, some data are available for two of the major toxicants: benzo[a]pyrene (B[a]P) and the tobacco-specific nitrosamines (*N*'-nitrosonornicotine [NNN] and NNK).

B[a]P, one of the earliest identified carcinogens in cigarette smoke, is a typical carcinogenic PAH and is often used as a surrogate index for the PAHs as a group. Efforts to reduce the levels of this carcinogen in smoke have included increasing the proportion of tobacco in the cigarette rod that is made up of reconstituted sheet, changing the tobacco blend, increasing the porosity of the

paper, and using other techniques (O'Connor et al. 2008; O'Connor and Hurley 2008; WHO 2008b; Rodgman and Perfetti 2009). Data are not available for all U.S. brands over time, but Hoffmann and Hoffmann (1997) published data for a prominent cigarette brand, measured repeatedly from 1959–1995, that showed a modest decline in B[a]P levels in smoke over that period.

In contrast to the decline in levels of B[a]P, levels of tobacco-specific nitrosamines, specifically NNK, increased dramatically in the previously referenced brand from 1978–1995 (Hoffmann and Hoffmann 1997). This increase was due in part to the increased nitrate levels in the tobacco used in cigarettes even before the curing (Hoffmann and Hoffmann 1997; Ding et al. 2008b; O'Connor et al. 2008; O'Connor and Hurley 2008; Rodgman and Perfetti 2009) and to changes in curing practices that have increased the presence of oxides of nitrogen and nitrate ion and the latter's reaction products during curing, with the resultant formation of tobacco-specific nitrosamines from the nicotine in the leaf (Hoffmann and Hoffmann 1997; NCI 2001; Peele et al. 2001; IARC 2004; Ding et al. 2008b; O'Connor et al. 2008; O'Connor and Hurley 2008).

Differences in Toxicant Yields Across Countries

Relatively more evidence is available for differences in toxicant yields from comparisons of international brands of cigarettes. Of particular note, the use of burley tobacco in U.S.-style blended cigarettes contributes substantially to the differences in tobacco-specific nitrosamines between U.S.-style cigarettes and those of Canada and Australia (Burns et al. 2008; Ding et al. 2008b; WHO 2008b), where most brands contain mainly unblended, flue-cured tobacco. Datasets are available for some smoke constituents that have been measured for major brands in the Canadian and Australian markets (WHO 2008b) and for a selection of international brands of blended cigarettes manufactured by Philip Morris (Counts et al. 2004, 2005).

Several other differences between Canadian and Australian brands were found, although cigarettes in both countries are made with unblended, flue-cured tobacco. Differences in the levels of cadmium and lead between the brands are notable. Figure 6.7 presents the mean yields of some toxic constituents for the major Canadian and Australian brands sampled in late 2000 to early 2001. The yields are normalized per mg of nicotine and expressed as a ratio to the mean yields for an international sample of brands manufactured by Philip Morris. The data for the Canadian brands are presented for all brands and for brands other than those with high NNN levels (U.S.-style and Gauloise cigarettes). The expected differences between flue-cured

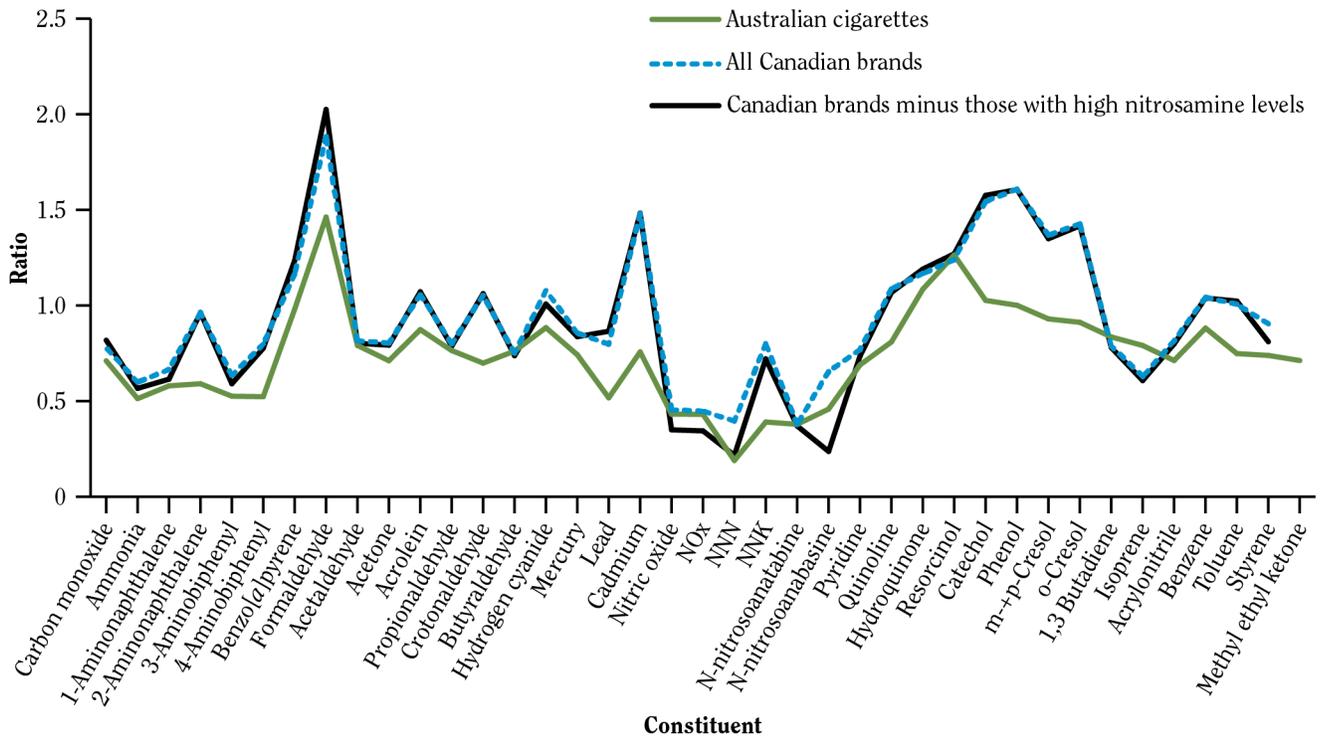
Table 6.2 Ratio of brand coefficient of variation to replicate measurement coefficient of nicotine and tar variation per milligram (mg), per Massachusetts Machine Smoking Protocol, in rank order

Per mg nicotine	Constituent	Per mg tar	Constituent
6.84	NNN	8.85	NNN
6.18	NAT	8.18	NAT
5.25	NAB	7.45	NAB
5.00	Mercury	6.28	Isoprene
4.79	Isoprene	6.07	Mercury
4.10	Benzene	4.86	Benzene
3.72	Acetone	4.36	Toluene
3.64	Toluene	4.33	Acetone
3.63	Propionaldehyde	4.30	HCN
3.59	HCN	4.21	Nitric oxide
3.59	Methyl ethyl ketone	4.19	1,3-Butadiene
3.47	Acetaldehyde	4.12	Propionaldehyde
3.43	1,3-Butadiene	4.11	Acetaldehyde
3.35	Acrolein	4.11	NNK
3.34	Nitric oxide	3.97	Methyl ethyl ketone
3.30	Phenol	3.78	Acrylonitrile
3.18	m + p-Cresol	3.76	3-Aminobiphenyl
3.12	NNK	3.49	Acrolein
2.91	Acrylonitrile	3.40	4-Aminobiphenyl
2.86	B[a]P	3.35	m + p-Cresol
2.79	Ammonia	3.23	2-Aminonaphthalene
2.45	3-Aminobiphenyl	3.18	Phenol
2.45	Hydroquinone	3.14	1-Aminonaphthalene
2.32	4-Aminobiphenyl	2.77	Styrene
2.27	2-Aminonaphthalene	2.59	Hydroquinone
2.24	Styrene	2.09	Ammonia
2.03	Crotonaldehyde	2.03	Cadmium
1.93	1-Aminonaphthalene	1.80	Butyraldehyde
1.93	Formaldehyde	1.78	Crotonaldehyde
1.90	Pyridine	1.75	Catechol
1.67	Butyraldehyde	1.73	Formaldehyde
1.46	Cadmium	1.66	B[a]P
1.44	Catechol	1.62	Pyridine
1.42	Lead	1.61	Lead
1.29	Arsenic	1.46	Quinoline
1.28	Quinoline	1.45	Arsenic

Source: Unpublished data from the 1999 Massachusetts Benchmark Study as provided by Greg Connolly, Massachusetts Department of Health.

Note: **B[a]P** = benzo[a]pyrene; **HCN** = hydrogen cyanide; **NAB** = *N'*-nitrosoanabasine; **NAT** = *N*-nitrosoanatabine; **NNK** = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; **NNN** = *N'*-nitrosornornicotine.

Figure 6.7 Ratio of the means of constituents in cigarette brands from Canada and Australia to the mean for an international sample of U.S.-style blended cigarettes manufactured by Philip Morris and sampled from late 2000 to early 2001



Source: Counts et al. 2005; World Health Organization 2008. Reprinted with permission from World Health Organization, © 2008.
 Note: NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN = N'-nitrosornicotine; NOx = nitrogen oxides.

and blended cigarettes are evident (Ding et al. 2008b); the flue-cured cigarettes from Australia and Canada have much lower levels of tobacco-specific nitrosamines (notably NNN and NNK) and substantially higher levels of B[a]P. Australian and Canadian brands, however, differ markedly from blended cigarettes in a number of other toxicants, with lower levels of oxides of nitrogen; 1-aminonaphthalene; 1,3-butadiene; and isoprene. Canadian, but not Australian, cigarettes have higher levels of catechol, phenol, and cresols. These differences may reflect the use of tobacco grown for use in cigarettes in different regions of Canada and Australia.

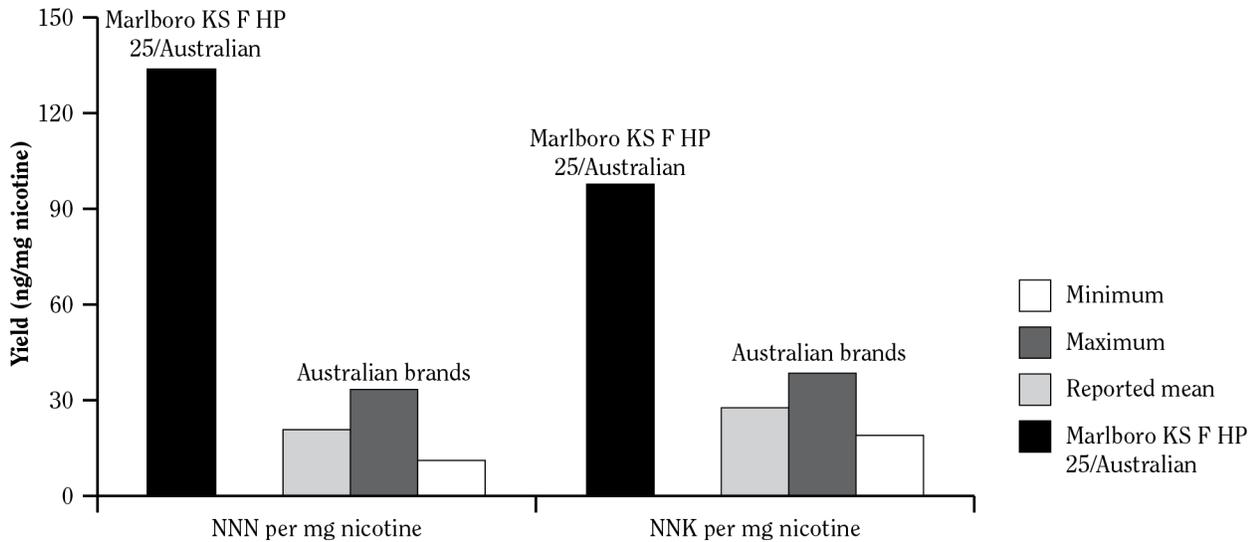
Figure 6.8 shows the differences in NNN and NNK between Australian brands and a blended version of the Marlboro brand designed for the Australian market (Burns et al. 2008; WHO 2008b). The levels of NNN and NNK in the blended-tobacco cigarette from Marlboro are much higher than those for even the highest level brand reported to the Australian regulatory authorities.

These differences in tobacco-specific nitrosamine levels in smoke translate to different exposures among smokers. Mouth-level exposures to NNN and NNK and urinary measures of NNAL—a metabolite of NNK—are higher among smokers in the United States than in smokers in Australia and Canada (Ashley et al. 2010), demonstrating that the observed differences in the composition of smoke result in substantive differences in exposure to tobacco-specific nitrosamines.

Low-Tar Cigarettes Do Not Reduce Risk of Lung Cancer

Early efforts to alter the risks of cigarettes focused on reducing the yields of tar and nicotine as measured by machine-smoking methods. As a result, machine-measured yields of tar and nicotine declined by more than 60% from the 1960s to 1990 (Hoffmann and Hoffmann 1997; NCI 2001). Much of that reduction was accomplished initially by adding filters and later by ventilating

Figure 6.8 Mean and range of *N*-nitrosornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) yields per milligram [mg] of nicotine for brands reported to the Australian government, contrasted with the levels of NNN and NNK reported for a Philip Morris Marlboro brand cigarette identified as an Australian brand, in 1999



Source: World Health Organization 2008b. Reprinted with permission from World Health Organization, © 2008.

Note: **F** = filter; **HP** = hard pack; **KS** = king size; **ng** = nanogram.

the filter to dilute the smoke coming through it, thus lowering the machine-measured yields of tar and nicotine so the newer products could be marketed as being less risky to health (NCI 2001). But to compensate for the reduced yields, smokers changed the way they smoked these cigarettes, resulting in no meaningful reduction in either the total dose of smoke received or in the risks of diseases caused by smoking (NCI 2001; USDHHS 2004). Changes in patterns included increasing the volume and velocity of puffs, increasing the duration of puffing, and shortening the intervals between puffs (NCI 2001). However, the protocol for smoking by machines was not changed.

Overall Death Rates for Lung Cancer Indicate Increased Risk of Smoking in Recent Decades

In the United States, the prevalence of smoking among males has declined since at least the 1950s, but age-adjusted death rates for lung cancer among men did not begin to decline until approximately 1990 (Wingo et al. 1999). Among women, the comparable death rates peaked around 2003 and significantly declined (Jemal et al. 2013), likely due to considerable success in reducing the prevalence of smoking among women. The long delay between decreases in the prevalence of smoking and changes in death rates for lung cancer raises the question

as to whether there might have been an increasing risk of lung cancer over time from smoking cigarettes that could have contributed to this delay.

Epidemiologic studies are a key source of evidence for assessing whether the risk of lung cancer associated with smoking has changed over time. Particularly informative is the comparison by Thun and Heath (1997) of two prospective cohort studies of the risk of smoking conducted by the ACS. Each study, conducted more than 20 years apart, followed more than 1 million men and women. The Cancer Prevention Study I (CPS-I) began in 1959, and the Cancer Prevention Study II (CPS-II) began in 1982. The more than two decades between the studies saw substantial changes in the design and composition of cigarettes and in the brands of cigarettes that Americans smoked. The decline in machine-measured yields of toxicants in cigarettes between these two studies led to an expectation that the risk of lung cancer death for smokers would likely be lower in the CPS-II. The authors compared death rates from lung cancer in the first 6 years of follow-up for each study among the subsamples of never and current smokers at enrollment. The risks were found to be higher in CPS-II (Thun and Heath 1997). Figure 6.9 presents the results from these analyses for men and women current smokers and never smokers based on 786,387

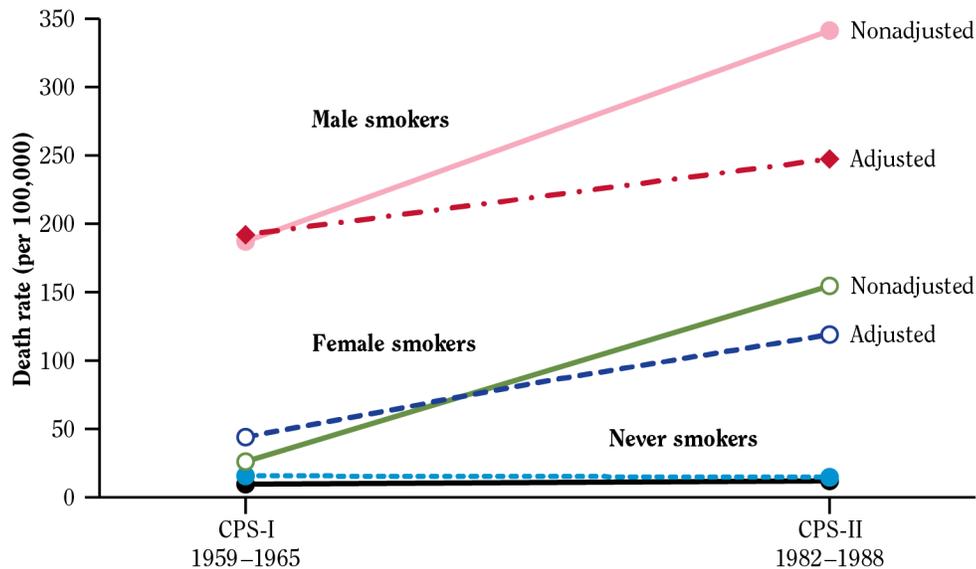
CPS-I and 711,363 CPS-II participants. The risk for never smokers (as measured by the death rate from lung cancer) went essentially unchanged during the interval between the two studies, but the risk for smokers increased dramatically, with a proportionately greater increase among women smokers. The increase in risk of death from lung cancer remained after controlling for measured differences in duration and intensity (number of cigarettes smoked per day) between the smokers in the two studies.

The 40-year follow-up of the British Doctors' Study from 1951–1991 presents similar evidence. During the second 20 years of follow-up, the risk of death from lung cancer was greater than during the first 20 years (Doll et al. 1994); this increase over time was limited to smokers and former smokers. Among never smokers, rates of lung cancer mortality were relatively constant across calendar years (Thun et al. 2006, 2008), suggesting that the changes observed in the relative risk (RR) of smoking were unlikely to have resulted from changes in population demographics or in other risk factors for lung cancer in the general population.

Models of risk based on smoking patterns have been applied to data on smoking prevalence for birth cohorts (i.e., sets of individuals born during specified calendar years and for whom rates can be examined as the cohorts

advance in age and calendar year) to estimate the expected occurrence of death from lung cancer in the absence of any change in the risk imposed by smoking. Using birth-cohort-specific data on smoking developed by Harris (1983) and a multistage carcinogenesis model similar to that developed by Whittemore (1988), Swartz (1992) predicted overall age-adjusted trends in lung cancer mortality for White men from 1970–1985. The author estimated that a 12% decline in rates should have occurred during this interval, based on the assumption of a constant effect over time. However, this estimated decline contrasted sharply with the observed 26% increase in lung cancer death rates during the interval (Swartz 1992). To predict death rates for lung cancer over time by birth cohort, Tolley and colleagues (1991) used an updated set of birth-cohort-specific estimates for smoking prevalence and a risk model developed by Peto (1986) that was based on data from the British Doctors' Study (Doll et al. 1994). These authors estimated that overall lung cancer mortality should have started to decline in the early 1980s for White men and in the mid-1990s for White women. Instead, observed lung cancer mortality continued to rise throughout the 1980s, peaking in the early 1990s for White men (Wingo et al. 1999) and 2003 for women generally (Jemal et al. 2013). A similar approach, using risk models developed from

Figure 6.9 Death rates from all lung cancers, by smoking status, Cancer Prevention Study I (CPS-I) and Cancer Prevention Study II (CPS-II), 1959–1965 and 1982–1988



Source: Thun and Heath 1997. Reprinted with permission from Elsevier, © 1997.

Note: All data are age adjusted. Data for male and female smokers are also adjusted for duration of smoking and number of cigarettes smoked per day. Each data point represents the mortality from the 6-year interval specified by the study.

the CPS-I data and birth-cohort-specific data on smoking prevalence from the National Health Interview Survey, demonstrated a systematic trend of increasing underestimation of observed death rates for lung cancer across all birth cohorts with advancing calendar years (NCI 2001).

Estimates of smoking behaviors for birth cohorts that incorporate changes in the number of cigarettes smoked per day were developed for NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) (Anderson et al. 2012). These estimates are more detailed than previous data on smoking behaviors for birth cohorts and include estimates of the intensity and duration of smoking for 5-year birth cohorts from 1900–1984. For each calendar year, these estimates provide rates of smoking initiation; prevalence of current and former smoking; and distributions of the duration of smoking, the duration of abstinence, and the number of cigarettes smoked per day for current and former smokers. These estimates for smoking behavior were combined with risk models for current, former, and never smokers derived from 12-year follow-up data from the CPS-I (Knoke et al. 2004, 2008) to estimate birth-cohort-specific lung cancer death rates from 1960–2000 (Burns et al. 2011b). The resulting estimates were compared with observed U.S. national lung cancer death rates for the same birth cohorts. The comparison showed a progressively increasing underestimation of U.S. national lung cancer death rates across all birth cohorts as calendar years advanced from the 1960s to 2000 (Burns et al. 2011b). This underestimation was eliminated when a term that increased the risk of smoking, based on the estimated duration of smoking after 1972, was added to the risk model. These analyses suggest that estimates of smoking-related lung cancer deaths that are based on observations in the 1960s underestimate the current risks of smoking, implying that the risk of death from lung cancer associated with smoking may have increased over the past several decades—that is, during the same decades in which changes in the design of cigarettes were made.

Considering the increase in risk of death from lung cancer seen from CPS-I to CPS-II, Thun and Heath (1997) recognized the possibility that the risk of death from lung cancer observed in CPS-I might underestimate the contributions of (a) amount smoked and (b) duration of smoking due to overreporting in the CPS-I data of the duration of smoking and the number of cigarettes smoked early in life. Among White men, the transition from other forms of tobacco use (e.g., cigars and pipes) to cigarettes began largely after 1914, because cigarette smoking was uncommon before that year (Burns et al. 1997). Because lung cancer is a disease of older ages, much of the lung cancer mortality experience in CPS-I occurred among men who were well past their adolescence by 1914, and yet many of them reported initiating smoking at early ages.

Some participants in CPS-I may have reported initiating cigarette smoking at the time at which they first used tobacco of any type, or they may have otherwise overestimated their duration of cigarette smoking, leading to a longer reported duration of cigarette smoking than actually occurred. The resulting misclassification, with a bias toward reporting a longer duration of smoking, could lead to a reduced magnitude of the estimated effect of duration of smoking on risk of lung cancer death in risk models based on CPS I data. Because a much larger fraction of those who developed lung cancer in CPS-II took up smoking after 1914, the effect of overreporting the duration of smoking would be lower in CPS-II, the magnitude of the estimated duration effect would increase, and the risk of smoking would appear to have increased between the two studies, with adjustment for differences in reported duration of smoking.

The study used the CISNET smoking rates and risk models based on CPS-I (Burns et al. 2011b) and attempted to minimize the contribution of overreporting of smoking duration and early smoking by eliminating birth cohorts born before 1915—the period during which overreporting was most likely. In addition, the potential for underestimation of the increase in duration over time to produce the observed progressive underestimation of the U.S. birth-cohort-specific death rates for lung cancer with advancing calendar time was examined by iteratively increasing the duration term and examining the fit of the resulting estimates to the observed U.S. death rates. Although increasing the duration term increased the estimated rates as anticipated, the pattern of a progressive change in risk remained even as calendar years advanced, with an overestimated actual risk giving way to an underestimated risk as calendar years advanced. Thus, an increasing effect of duration on risk of death from lung cancer did not explain the progressive underestimation of mortality from lung cancer, whereas a term increasing the risk of cigarette smoking over time did.

Overreporting in CPS-I also may have resulted in an overestimation of the number of cigarettes smoked early in life, but the contribution of cigarettes smoked per day to risk of lung cancer is much smaller than the contribution of duration (Flanders et al. 2003; Knoke et al. 2004), and the exponent for the cigarettes-per-day term in the CPS-I risk equations is close to one (Knoke et al. 2004, 2008). As a result, any underestimation of lifetime number of cigarettes smoked per day due to overreporting of smoking early in life is expected to be modest and could be approximated by a constant that would be incorporated in the risk equations when they are adjusted for the healthy population selection bias (Pinsky et al. 2007) required for such estimates (Tolley et al. 1991; Burns et al. 2011b).

To further assess changes in the risk of lung cancer from smoking over time, Thun and colleagues (2013) extended their analyses by comparing the lung cancer risk associated with smoking observed in five contemporary cohorts (2000–2010) with risks observed in CPS-I (1959–1965) and CPS-II (1982–1988). For never smokers, rates of death from lung cancer remained constant across time among men and increased only slightly among women. Among females 55 years of age and older at baseline, the RR for lung cancer comparing current smokers to never smokers progressively increased from 2.73 in CPS-I to 12.65 in CPS-II to 25.66 for the 2000–2010 cohorts. Corresponding RRs for current male smokers were 12.22, 23.81, and 24.97, respectively. Compared with their counterparts in CPS-I and CPS-II, both men and women in the contemporary cohorts were at greater risk for lung cancer despite smoking fewer cigarettes per day. Duration of smoking increased substantially across the study time periods for women. In comparison, duration of smoking changed only modestly for men across the studies and actually declined slightly between CPS-II and the 2000–2010 cohorts.

Thun and colleagues (2013) also stratified their analyses by smoking intensity (i.e., number of cigarettes smoked per day) and duration of smoking for all three study periods. Within each stratum of smoking intensity and duration of smoking, the RR estimates increased over time for women. For men, RR estimates increased over time within each stratum of smoking intensity, but a consistent pattern was not evident for each stratum of smoking duration. The authors concluded that the risk of lung cancer from smoking has continued to increase among women but among men has plateaued at the very high levels observed in the 1980s.

Trends in most other tobacco-related cancers have not been examined in detail, although Baris and colleagues (2009) reported an increase in the incidence of bladder cancer over the past several decades.

Changes Over Time in the Types of Lung Cancer Associated With Smoking

Adenocarcinoma of the lung has been increasing in the United States since the 1970s (Travis et al. 1996; Wingo et al. 1999), as manifested in rising incidence rates and an increasing proportion of all lung cancers that are adenocarcinomas (Wingo et al. 1999; Devesa et al. 2005). Theoretically, this increase could be due to changes over time in the classification of tumors, but an analysis by Charloux and colleagues (1997) found the increase to

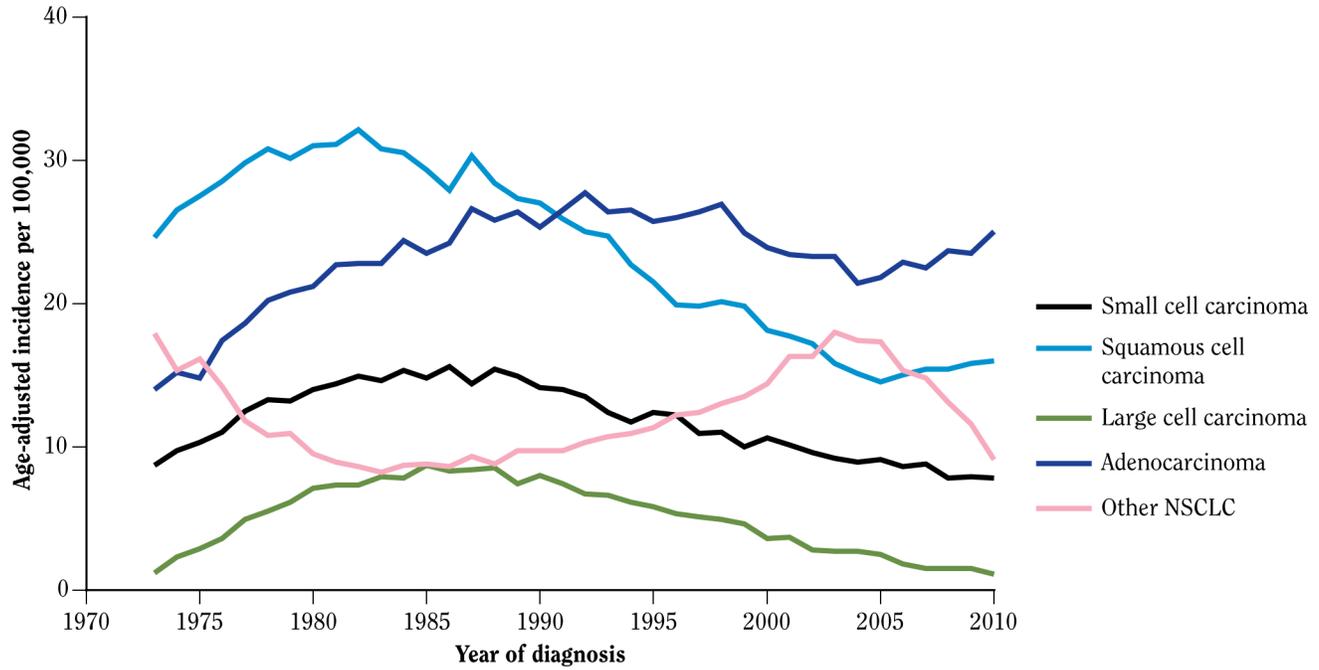
be real and not a consequence of changing diagnostic practices.

Notably, the increase in adenocarcinoma of the lung has been accompanied by an increase in the estimated RR for this type of lung cancer associated with cigarette smoking. Early in the investigation of the lung cancer epidemic, the most common histologic type of lung cancer in men was squamous cell carcinoma, and the RR of squamous cell carcinoma associated with smoking was substantially higher than that for adenocarcinoma (Wu-Williams and Samet 1994; USDHHS 2004). Kreyberg (1962) even debated whether adenocarcinoma was associated with cigarette smoking, because of the low RR and because adenocarcinoma is the most common type of lung cancer among women who have never smoked. As the incidence of lung adenocarcinoma increased over time, the RRs of this type of lung cancer associated with smoking also increased (USDHHS 2001), suggesting that a new, or at least a substantially enhanced, risk of developing adenocarcinoma of the lung occurred in smokers. In a comparison of data from CPS-I and CPS-II, Thun and colleagues (1997) found that the RR for adenocarcinoma increased in smokers from 4.6 for men and 1.5 for women (per data from CPS-I, conducted 1959–1965) to 19.0 for men and 8.1 for women (per data from CPS-II, conducted 1982–1988), but that the age-adjusted death rates for adenocarcinoma of the lung among never smokers were essentially unchanged over the period. Furthermore, risk for lung cancer of all tissue types among never smokers remained constant over the same interval (Thun et al. 2006, 2008).

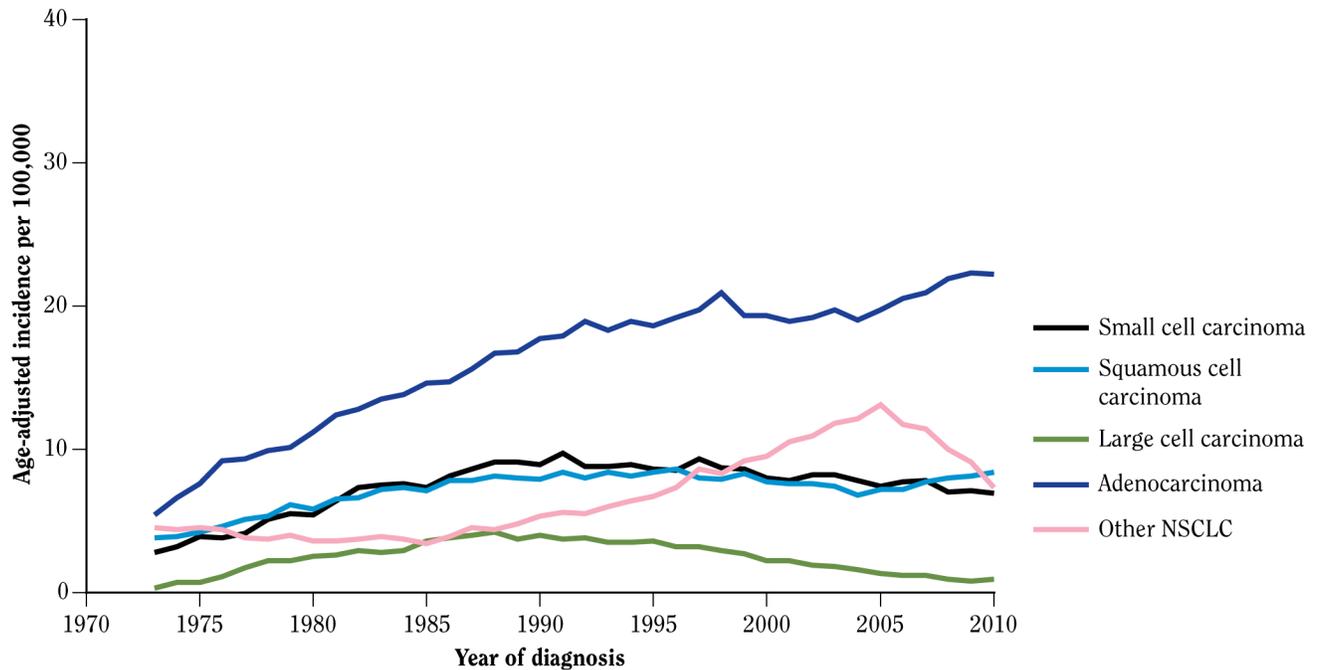
Trends across calendar years in age-standardized incidence rates of lung cancer have also varied by tumor type. Figure 6.10 presents trends in age-standardized incidence rates in the United States from 1973–2010 for lung cancer by gender and histologic type using data from NCI's SEER Program. Among men, the decline in the incidence rate of squamous cell carcinoma started well ahead of the decline for incidence rates for adenocarcinoma; similar trends are seen for women. Rates of squamous cell and small cell carcinoma have been declining in men since the early- to mid-1980s, but rates of adenocarcinoma did not peak until the 1990s (Travis et al. 1996; Wingo et al. 1999; Devesa et al. 2005). Age-standardized rates in women reflect their later uptake of smoking, resulting in a later year of peak smoking-induced rates of lung cancer, and the patterns are more difficult to interpret. However, rates of squamous cell carcinoma leveled off among women around 1990, but their rates of adenocarcinoma continued to increase through the 1990s (Wingo et al. 1999; Devesa et al. 2005). The recent trends in rates for the NSCLCs have been affected by trends in diagnostic practice,

Figure 6.10 Standardized incidence of lung cancer, by gender and histology (age adjusted to 2000 U.S. population), 1973–2010

A. Males



B. Females



Source: Surveillance, Epidemiology, and End Results (SEER) Program, public use data.

Note: Other non-small-cell-lung carcinoma (NSCLC) includes code 8046 from the SEER Registry, as well as others. In the most recent years (2001–2010), most of the “Other NSCLC” were 8046. Before 2001, most “Other NSCLC” were coded as 8010 “Carcinoma, NOS.” Around 2004 there were changes in how lung cancers were coded in the SEER Registry data (Travis et al. 2004, 2011; Johnson et al. 2007). There were also advances in diagnosis and treatment around 2004 (erlotinib or gefitinib for patients with *EGFR* mutations, bevacizumab for patients with non-squamous NSCLC) that make accurate histologic classification important (Langer et al. 2010; Kulesza et al. 2011; Conde et al. 2013).

reflecting treatment approaches that are targeted by histologic type. There has been a trend to avoid nonspecific classification and to designate lung cancers as adenocarcinoma and squamous cell carcinoma (Langer et al. 2010; Travis et al. 2011; Conde et al. 2013).

Interpreting age-standardized rates of lung cancer is difficult because of variations in the prevalence of smoking, in the distribution of duration of smoking, and in the distribution of the duration of abstinence in the U.S. population over the past several decades. For that reason, rates of lung cancer by histologic type have also been examined by birth cohorts. This approach examines outcomes as the population born during the selected calendar years initiates and quits smoking over time (and ages, as well). These two smoking behaviors have been found to differ substantially across sequential birth cohorts for the U.S. population (Burns et al. 1997, 2011b).

Zheng and colleagues (1994) found that birth-cohort-specific rates of lung cancer by histologic type across calendar years in the Connecticut Tumor Registry data demonstrated a clear birth-cohort pattern for increased rates of adenocarcinoma; that is, there were identifiable differences in rates by cohort. These changes paralleled gender and generational changes in smoking rather than advances in diagnostic procedures (Thun et al. 1997a). In this Connecticut study, the birth-cohort trends for squamous cell carcinoma were consistent with changes in smoking prevalence by birth cohort over time, but rates of adenocarcinoma by birth cohort progressively increased for both men and women in a manner that was not consistent with changes in smoking prevalence by birth cohort (Zheng et al. 1994). This increase was consistent with an increase over time in the risk of adenocarcinoma associated with smoking due to changes in the design of cigarettes, including the introduction of filters and low-tar cigarettes (Zheng et al. 1994; Thun et al. 1997a).

Figures 6.11 and 6.12 present incidence rates for lung cancer by histologic type based on 5-year birth cohort data from the SEER Program. Although the proportion of lung cancer that is adenocarcinoma is somewhat higher for women across all birth cohorts, a trend is found in which adenocarcinoma represents an increasing proportion of lung cancer when sequential cohorts are examined for both men and women. Data in Figures 6.11 and 6.12 are combined in Figure 6.13 to present mean values for the proportions of all lung cancers with a designated histologic type that were adenocarcinoma for those cohorts with data available. The mean values demonstrate a substantial increase in the proportion of lung cancer that is adenocarcinoma when moving from the earliest to the more recent cohorts. An important caveat in interpreting these means is that the age range for each cohort is

different, as it must be, with the earliest cohorts having only the older age ranges and the more recent cohorts only the younger age ranges.

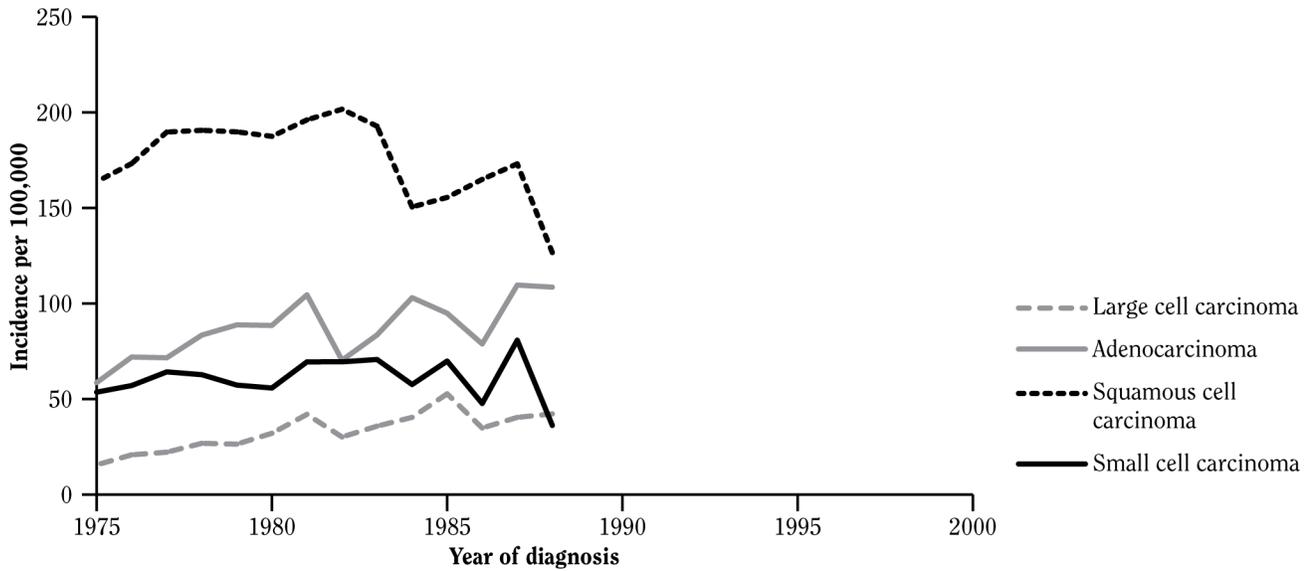
Data from the SEER Program do not contain information about smoking status at the individual level, but the birth-cohort rates for the different histologic types presented in the figures result from a steadily progressing mixture of current, former, and never-smoking behaviors that are specific for each cohort as it moves forward in time. Therefore, differences in the proportion of lung cancers due to a specific histologic type are not due to differences by histology in overall smoking behaviors, given that these behaviors are the same for all of the histologic types in any given calendar year. Differences by histologic type within a cohort can reflect differences in the relationship of age to histologic type, differences in the rate of decline in risk after smoking cessation for the different histologies, or variation in the exposures over time in the agents causing the different types of lung cancer.

Effects due to aging, such as those that might be manifested if the durations of smoking required to produce squamous cell carcinoma and adenocarcinoma are different, would likely reveal themselves in a similar fashion across all cohorts as those cohorts reach the appropriate ages, but Figures 6.11 and 6.12 do not indicate a consistent pattern with age.

The time course of reduction in excess risk of lung cancer after cessation of smoking likely differs for the different histologic types. For example, some data suggest that excess risks for squamous cell and small cell lung cancers may decline more rapidly after cessation than do excess risks for adenocarcinoma (Kenfield et al. 2008). As calendar years have advanced, the U.S. population in the age groups at substantial risk for lung cancer (i.e., those over 50 years of age) is composed of an increasing fraction of former smokers, and those former smokers have had longer durations of abstinence. The potential effect of a slower decline in risk for adenocarcinoma raises the possibility that the decline in squamous cell carcinoma and the increase in adenocarcinoma over time may be a result of a relatively more rapid decline in risk for squamous cell carcinoma, leaving an increasing fraction of lung cancer as adenocarcinoma. However, if the increasing proportion of lung cancer that is adenocarcinoma was in fact due to this effect (of a less rapid decline in the excess risk for adenocarcinoma following cessation), then the greatest shift would be in the earliest birth cohorts, among whom the effects of differences in risk with abstinence would be most evident. Figures 6.11 and 6.12 show the opposite pattern—the greatest increase in the proportion of lung cancer that is adenocarcinoma occurs in the more recent birth cohorts who are younger in age and have less cumulative abstinence.

Figure 6.11 Incidence of lung cancer among U.S. men from various birth cohorts, by histologic type (adenocarcinoma, squamous cell carcinoma, and small and large cell carcinoma) and year of diagnosis, 1975–2000

A. Birth cohort: 1900



B. Birth cohort: 1905

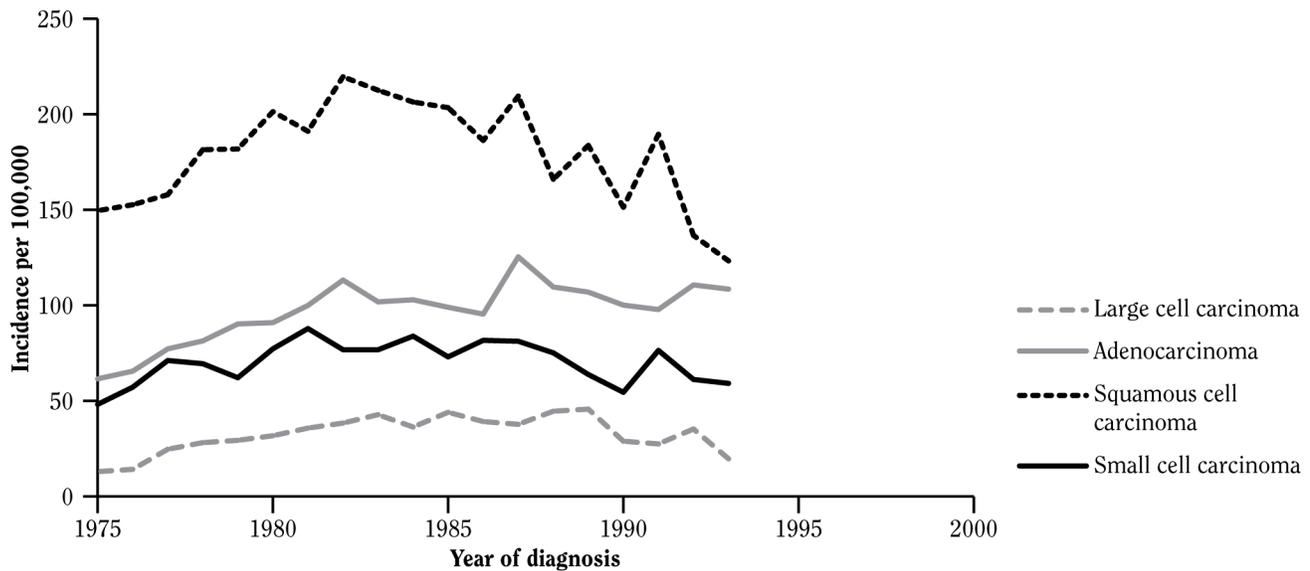
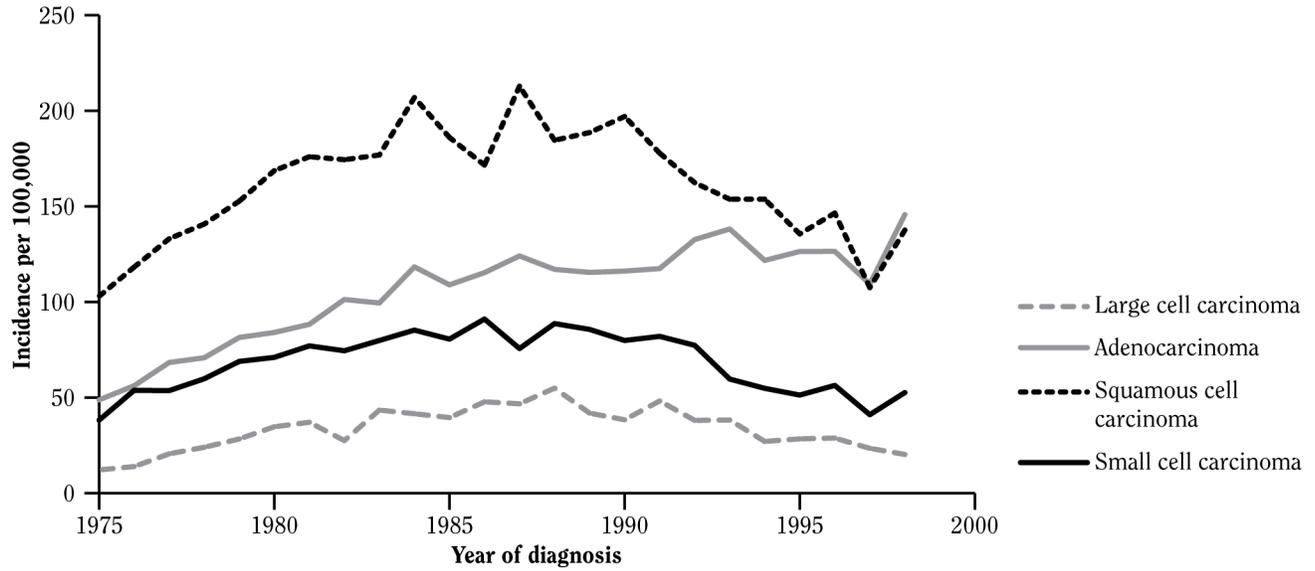


Figure 6.11 Continued

C. Birth cohort: 1910



D. Birth cohort: 1915

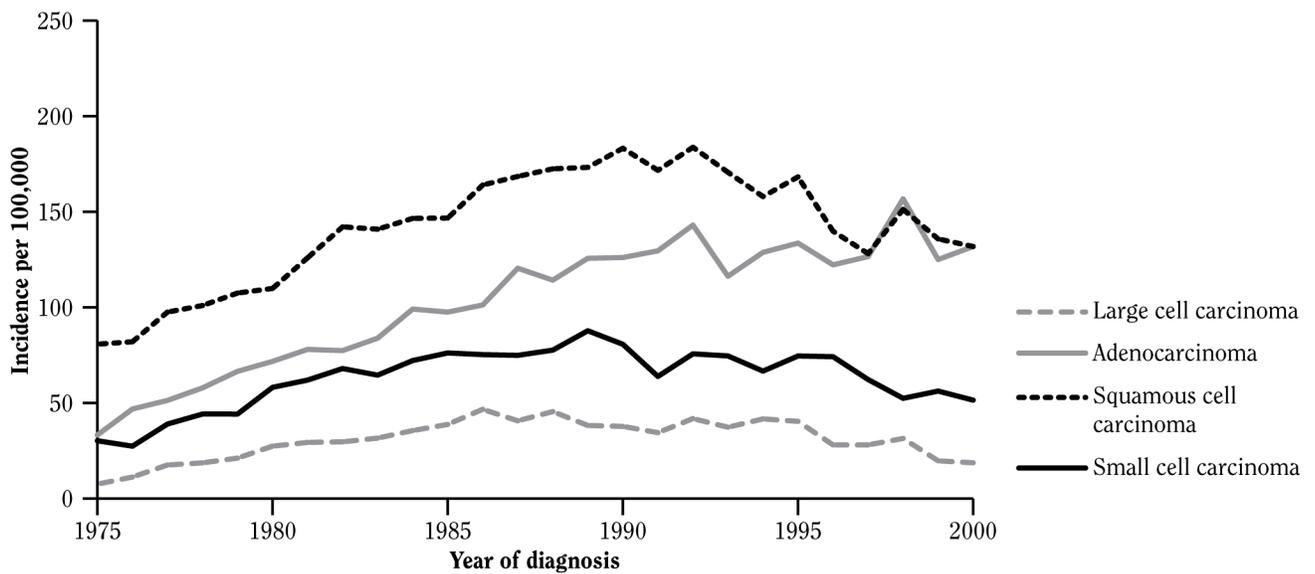
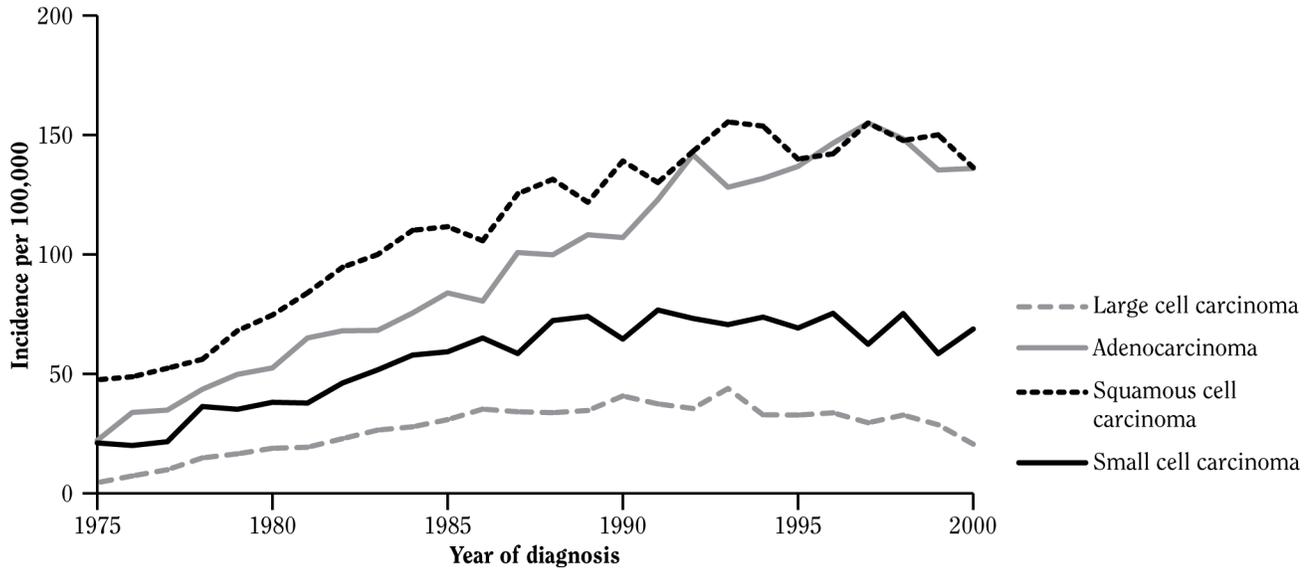


Figure 6.11 Continued

E. Birth cohort: 1920



F. Birth cohort: 1925

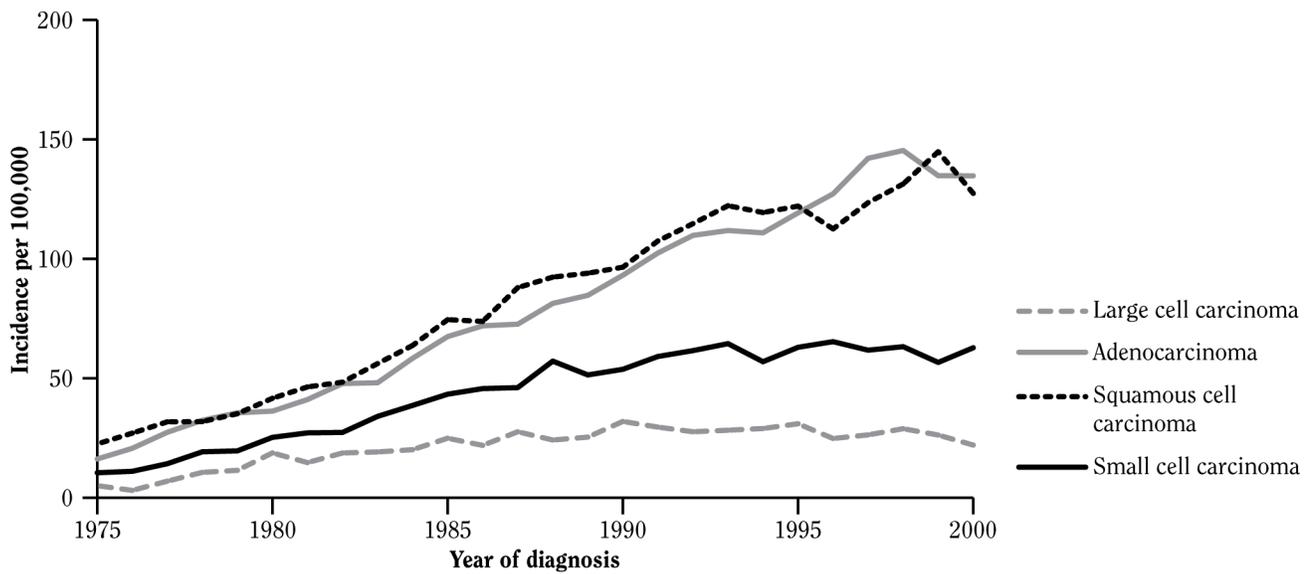
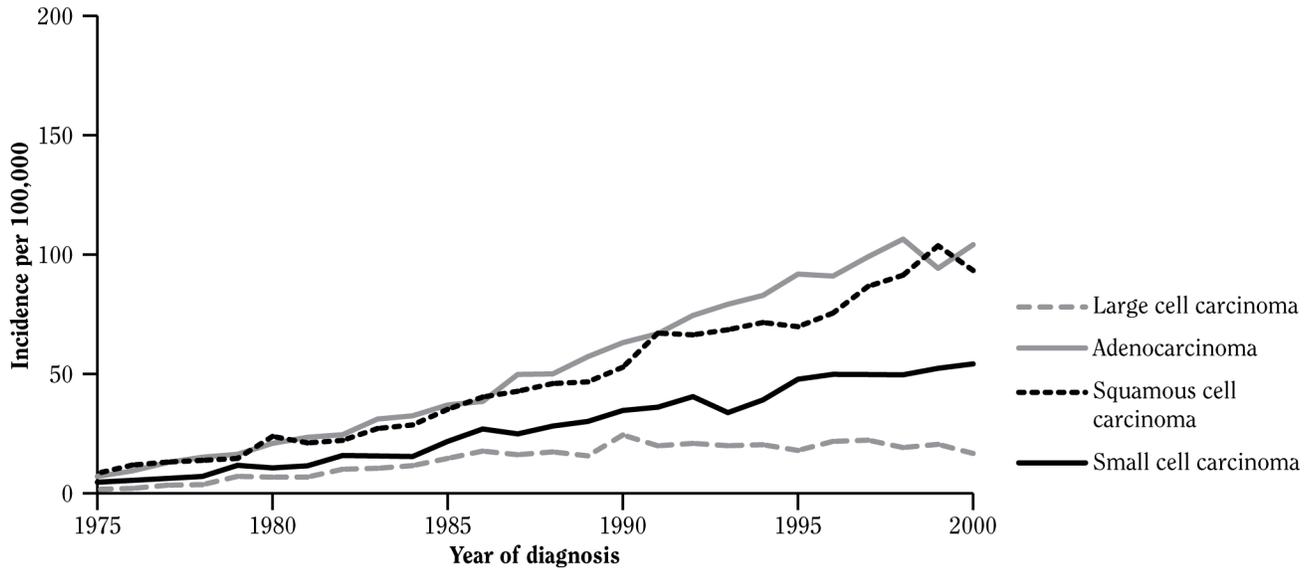


Figure 6.11 Continued

G. Birth cohort: 1930



H. Birth cohort: 1935

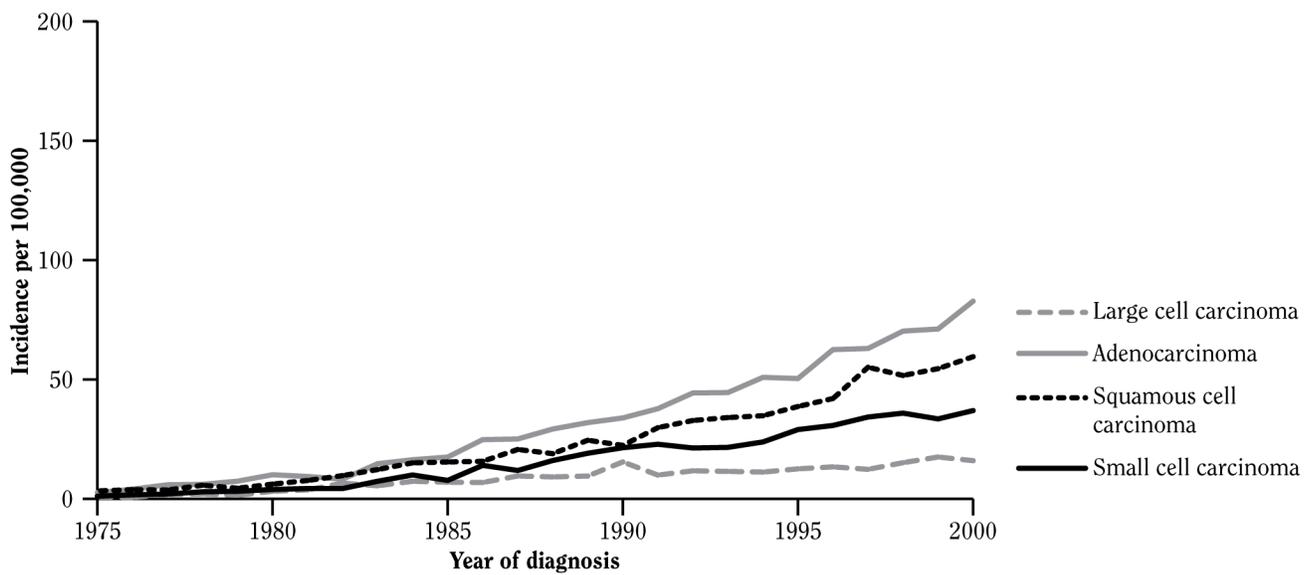
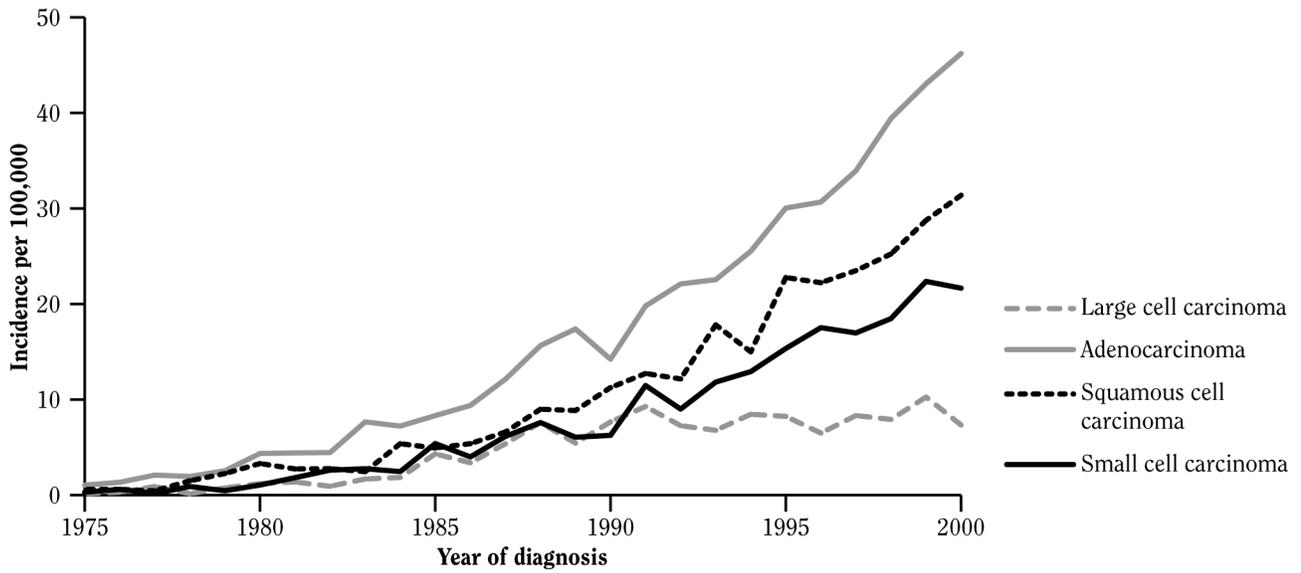


Figure 6.11 Continued

I. Birth cohort: 1940



J. Birth cohort: 1945

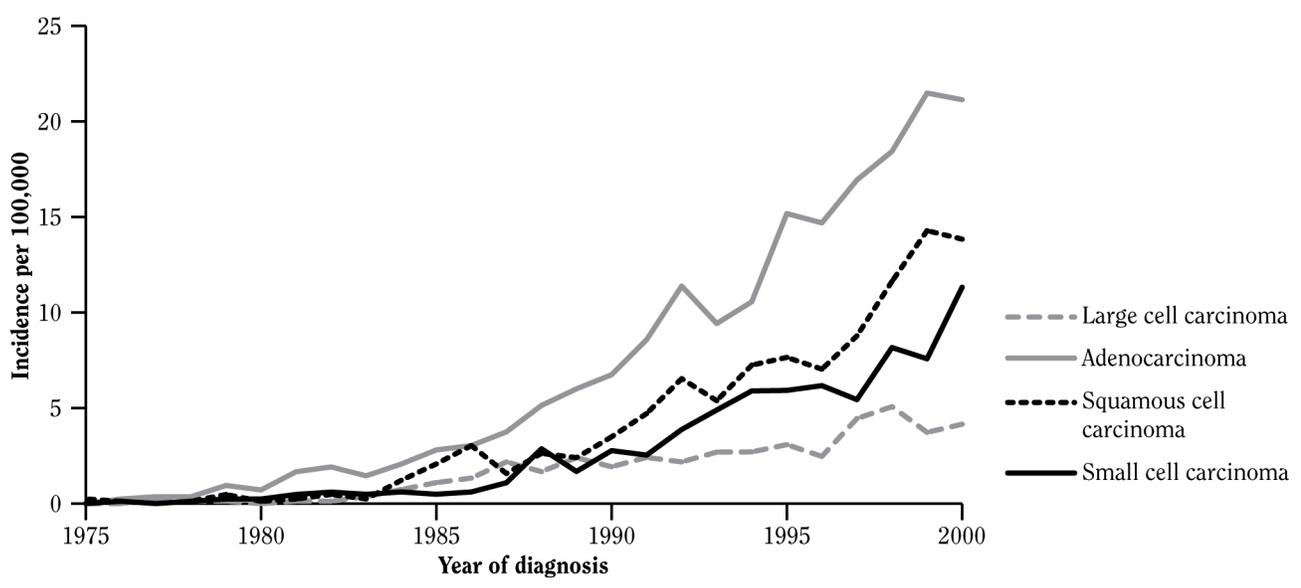
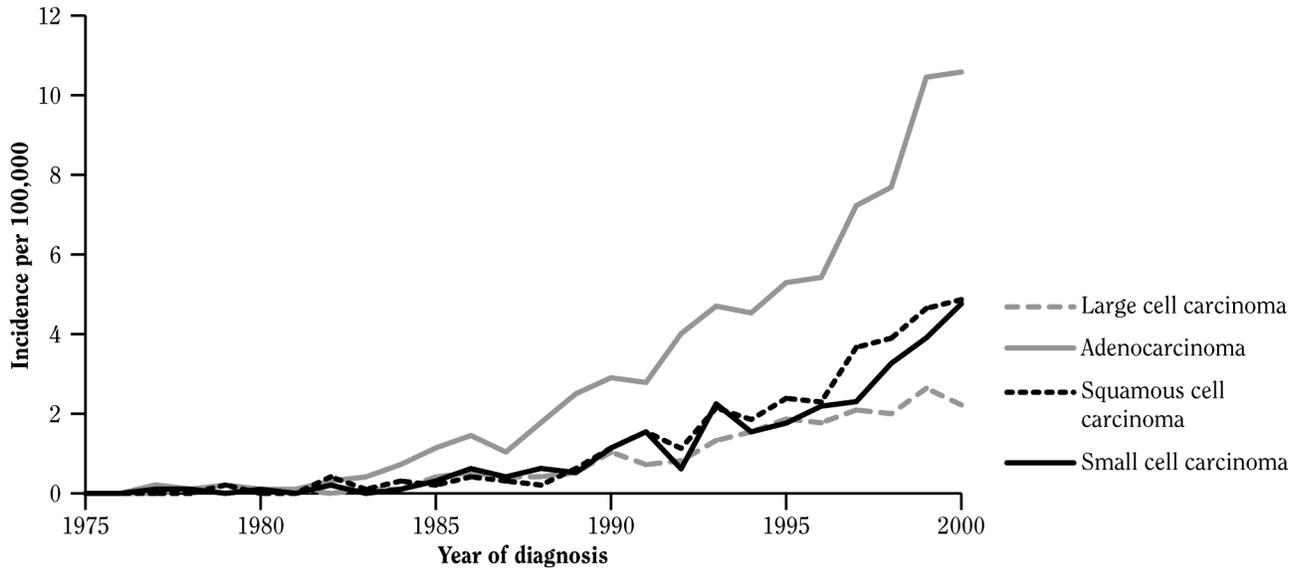
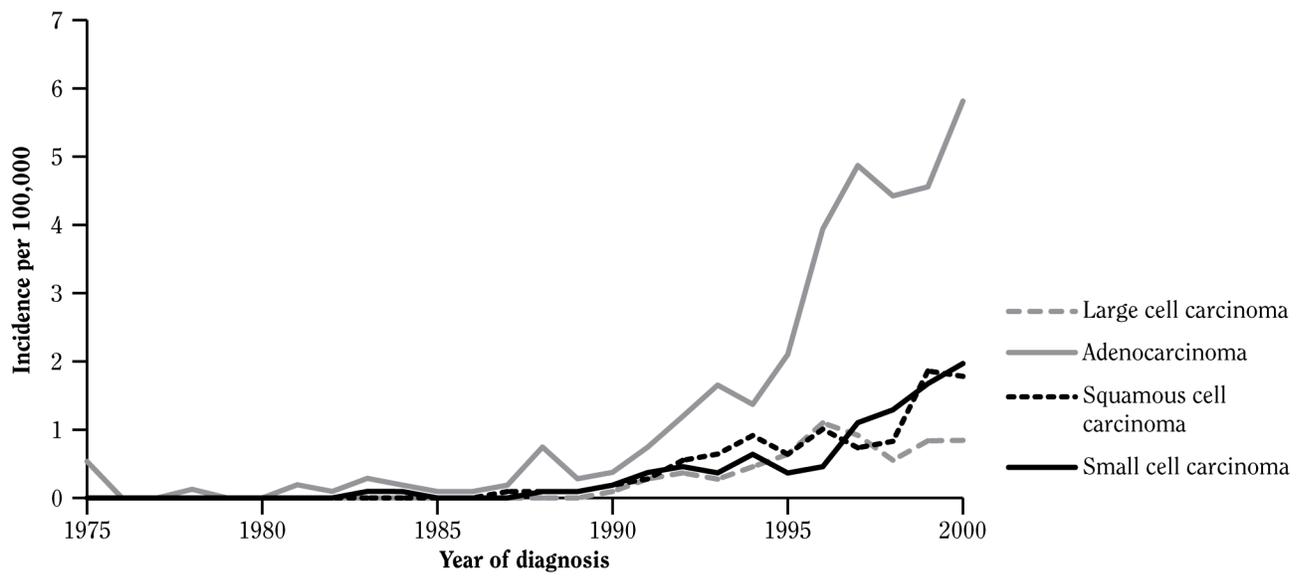


Figure 6.11 Continued

K. Birth cohort: 1950



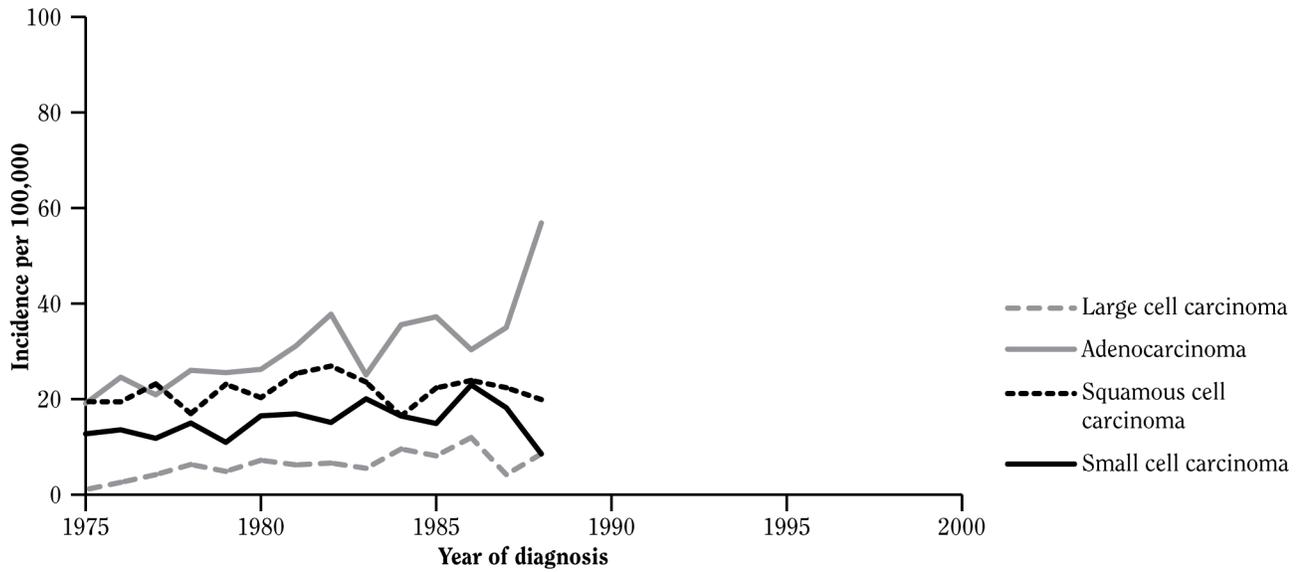
L. Birth cohort: 1955



Source: Surveillance, Epidemiology, and End Results Program, public use data.

Figure 6.12 Incidence of lung cancer among U.S. women from various birth cohorts, by histologic type (adenocarcinoma, squamous cell carcinoma, and small and large cell carcinoma) and year of diagnosis, 1975–2000

A. Birth cohort: 1900



B. Birth cohort: 1910

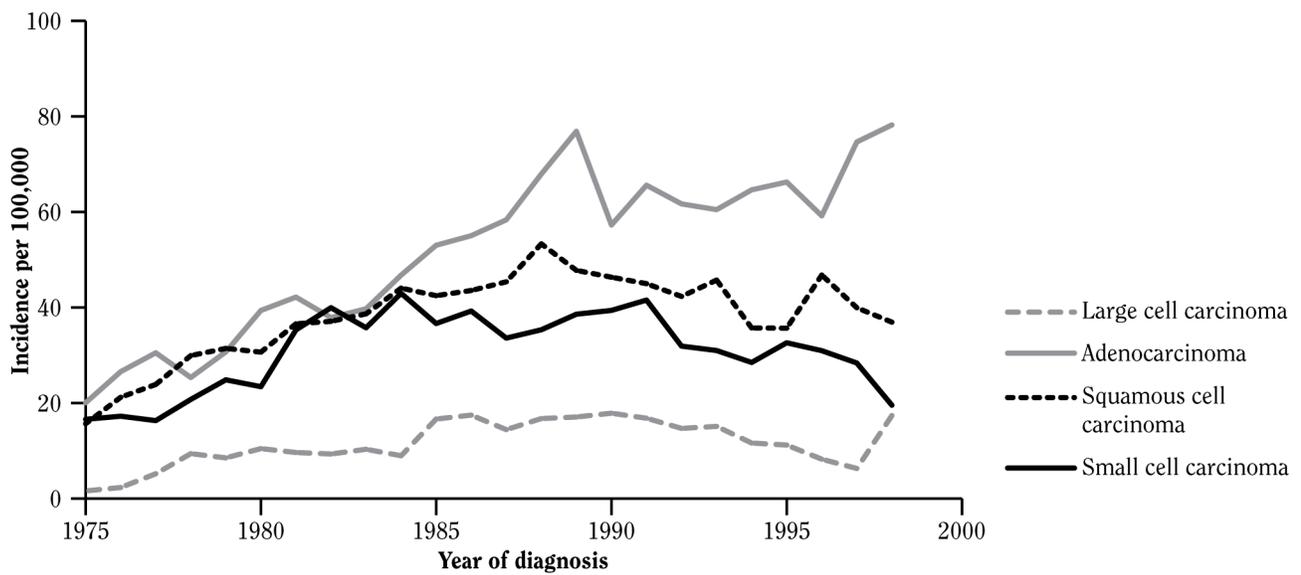
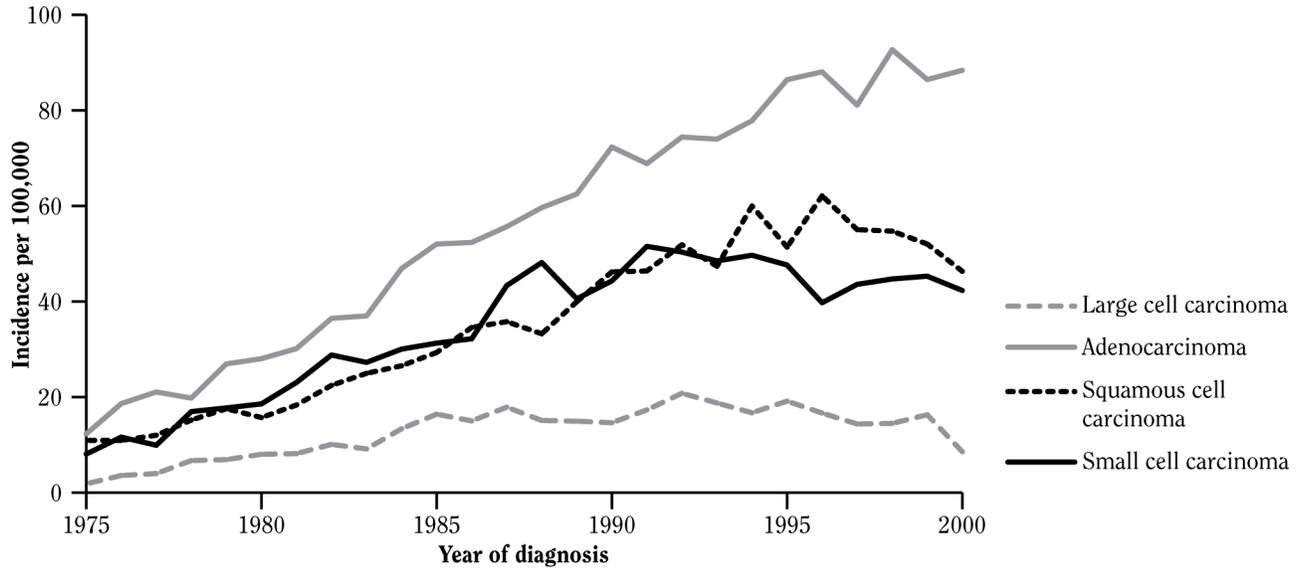


Figure 6.12 Continued

C. Birth cohort: 1920



D. Birth cohort: 1925

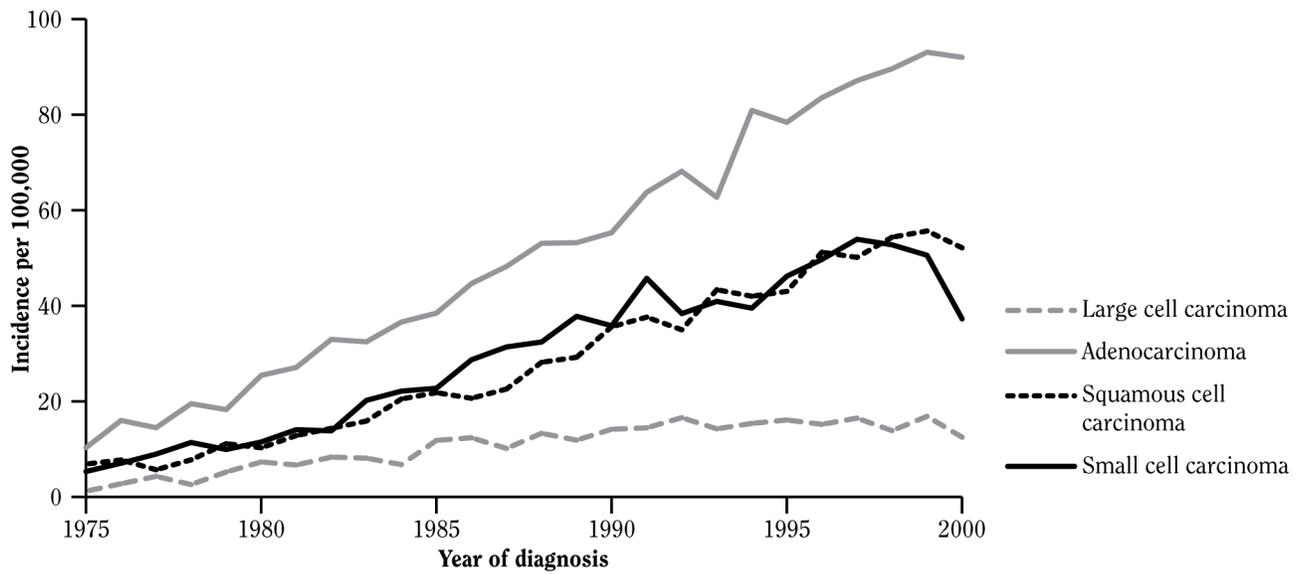
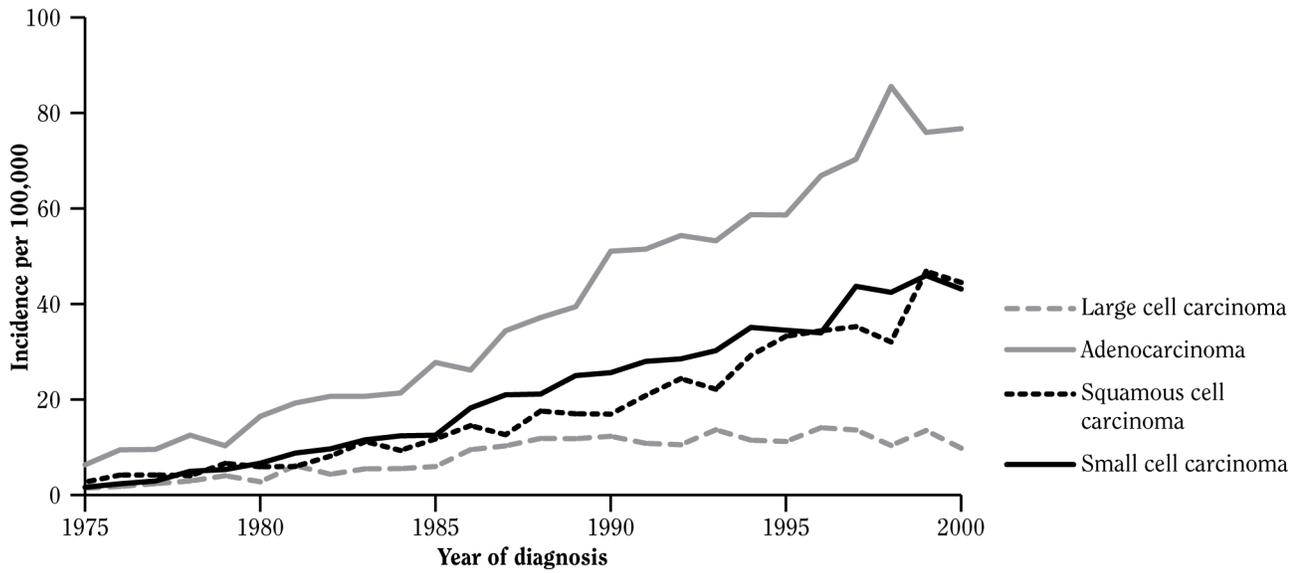


Figure 6.12 Continued

E. Birth cohort: 1930



F. Birth cohort: 1935

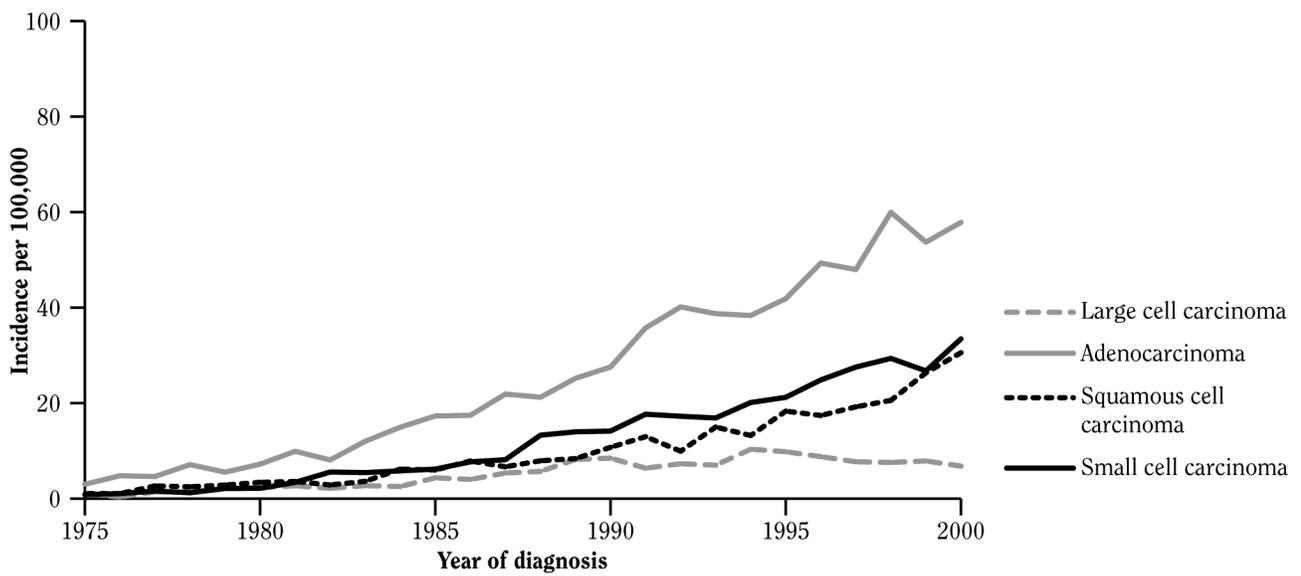
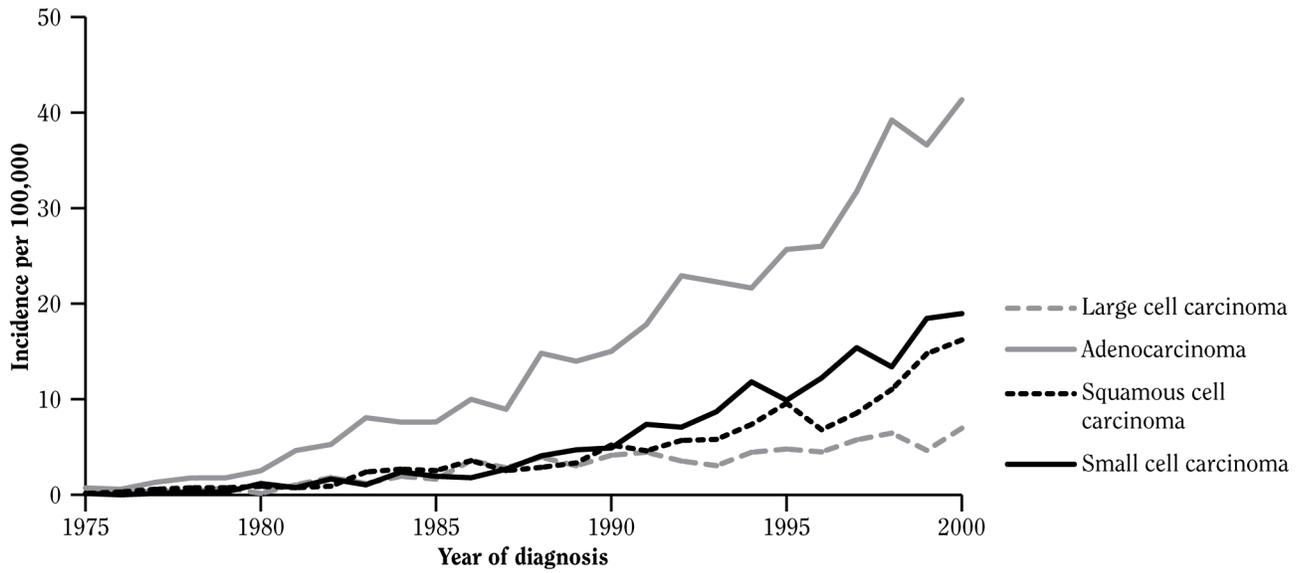


Figure 6.12 Continued

G. Birth cohort: 1940



H. Birth cohort: 1945

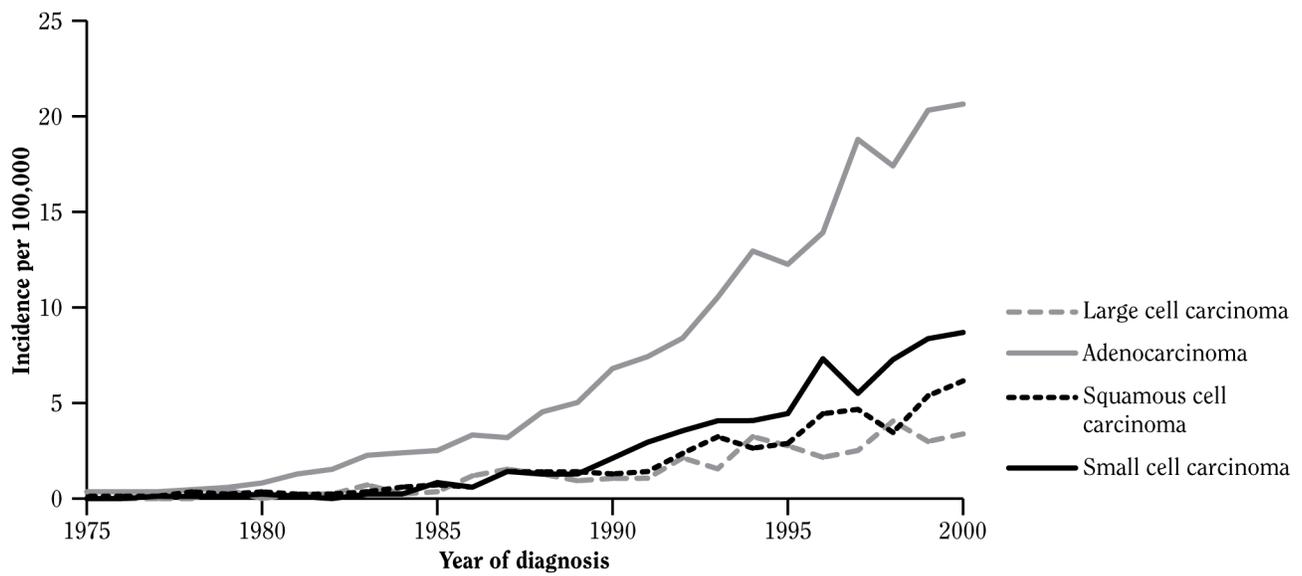
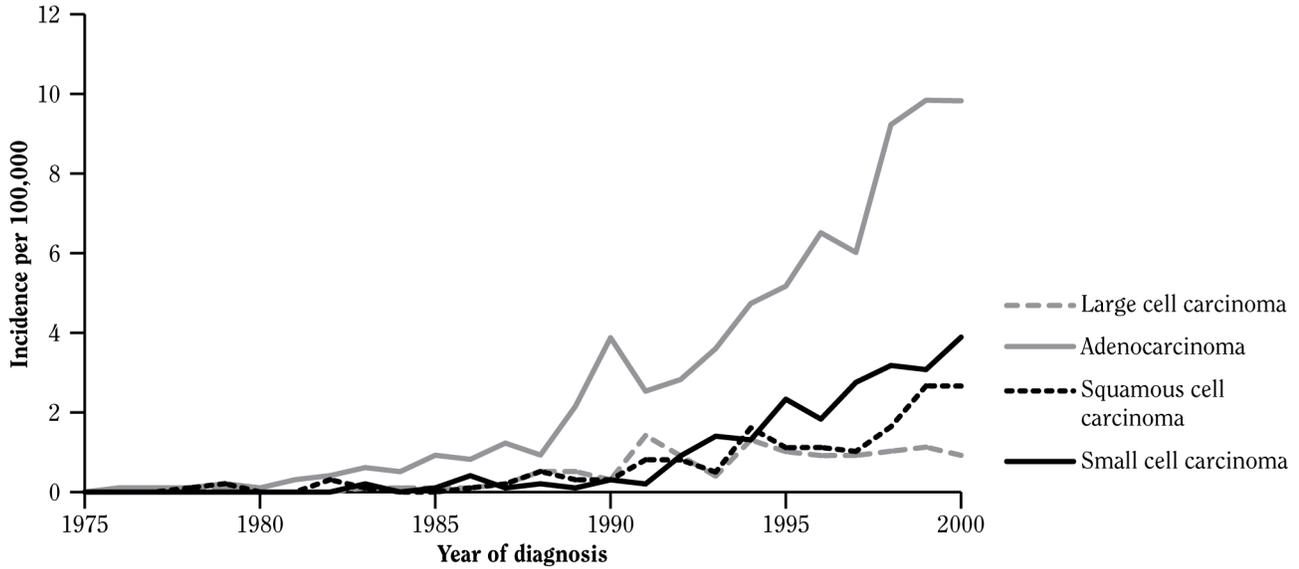
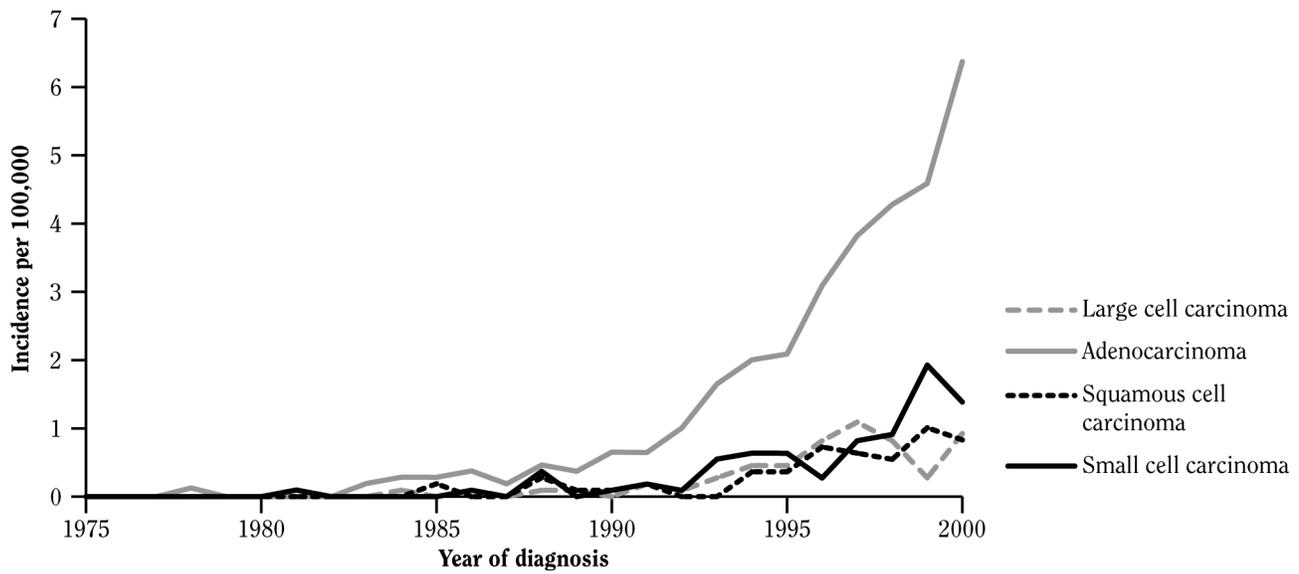


Figure 6.12 Continued

I. Birth cohort: 1950



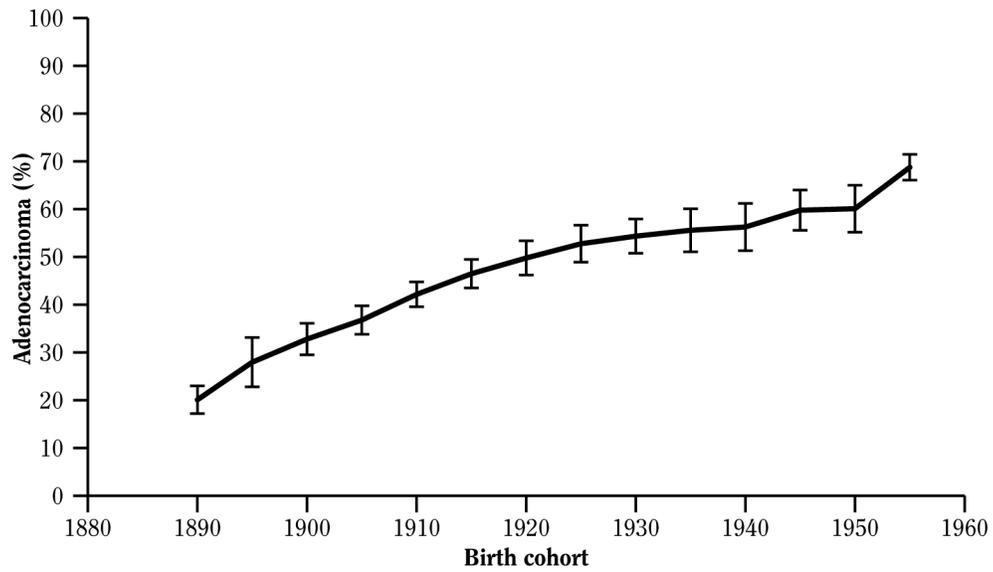
J. Birth cohort: 1955



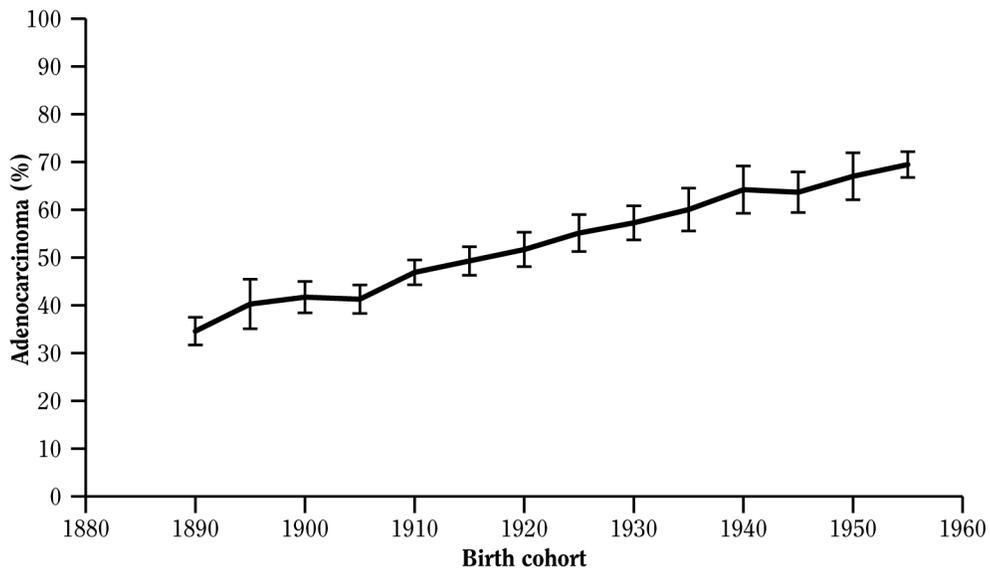
Source: Surveillance, Epidemiology, and End Results Program, public use data.

Figure 6.13 Unweighted mean percentage of all lung cancers that were adenocarcinoma, by gender and birth cohort for the available calendar years, United States, 1890–1955

A. Males



B. Females



Source: Surveillance, Epidemiology, and End Results Program, public use data.

The birth-cohort pattern observed in Figures 6.11 and 6.12 suggests that changes in the design and composition of cigarettes may be a factor that is driving the increase in rates of adenocarcinoma (Charloux et al. 1997; Thun et al. 1997a; NCI 2001). Risk of lung cancer reflects cumulative exposure to cigarette smoke, and if a change in the design or composition of cigarettes increases the risk of lung cancer from smoking, then the onset of increasing risk begins at the time when the change is made. Each succeeding cohort would have a larger fraction of its cumulative smoking exposure from the new cigarettes, as existing brands are refashioned and smokers switch to brands with greater risk characteristics. This increased risk becomes stronger in successive birth cohorts, particularly if use of the newer, more hazardous product is more common among younger than older smokers. Among older individuals from the earlier birth cohorts, rates of lung cancer will continue to be dominated by the substantial contribution of their past smoking, and an increase in risk resulting from a more recently changed cigarette product will make a relatively modest proportional contribution to the pre-existing and already substantial risk for these cohorts. As more recent birth cohorts are examined, the onset of increasing risk due to a change in product design will begin at an earlier age because members of the cohort will begin smoking the newer products at a younger age. The increment in risk with the use of the newer products reflects a larger proportion of the total risk for the cohort, simply because the duration of smoking preceding the shift to a more dangerous type of cigarette is shorter and thus the risk for that earlier period as a fraction of total risk is smaller. Such an effect could explain the progressive increase in the proportion of lung cancers that are adenocarcinomas across sequential cohorts, as shown in Figure 6.13.

Differences in the prevalence of current and former smoking and differences in the distribution of the duration of smoking and the duration of abstinence from smoking vary markedly across birth cohorts and contribute to differences in risks of lung cancer. To account for these differences in the examination of rising rates of adenocarcinoma, birth-cohort-specific smoking behaviors have been used to model changes in the rates of lung cancer of different histologic types (Burns et al. 2011a), as was done for overall lung cancer mortality and incidence rates. Risk models derived from CPS-I were applied to the smoking behaviors of birth cohorts. These behaviors include rates of smoking initiation, prevalence of current and former smoking, and distributions of the duration of smoking, duration of abstinence, and number of cigarettes smoked per day for current and former smokers (Burns et al. 2011a). The resulting rates were adjusted for a healthy

population selection bias and differences between rates of incidence and mortality and then were scaled, based on the fraction of lung cancers of the appropriate histologic type in the SEER Program data for the first years available (1973–1975).

The predicted rates for squamous cell carcinoma and adenocarcinoma by 5-year birth cohort were compared with the rates observed in data from the SEER Program for the same cohorts during the calendar years 1973–2000. For squamous cell carcinoma, the predicted rates closely matched the rates from the SEER Program, suggesting that much of the variability in the incidence rates of squamous cell carcinoma over the past several decades can be explained by changes in the rates of smoking prevalence and cessation. In contrast, the predicted rates for adenocarcinoma did not match data in the SEER Program, and the differences between predicted rates and those of the SEER Program varied systematically by birth cohort. When a term increasing the risk for adenocarcinoma with duration of smoking after 1950 was added to the risk model for current and former smokers (to simulate an increasing risk over time associated with a change in the design of cigarettes), the predicted rates matched the rates from the SEER Program. Thus, these analyses suggest that increasing risk of lung cancer over time may be associated with changes in the design or composition of cigarettes. The analyses also raise the possibility that the increase in overall lung cancer mortality from smoking may reflect an increase in the risk of developing adenocarcinoma from smoking, with little change in the risk of developing squamous cell carcinoma.

Some researchers have suggested alternative explanations for the increase in lung adenocarcinoma. Based on birth-cohort analyses of data from the SEER Program and differences in the temporal trends in the incidence of squamous cell lung cancer and adenocarcinoma of the lung, Chen and colleagues (2007b,c, 2009) suggested an effect of air pollution, and specifically nitrogen oxides, as the cause for the trends in adenocarcinoma. However, because among never smokers both lung cancer mortality and the incidence of adenocarcinoma do not seem to have changed over time and because the risk of adenocarcinoma among smokers has increased, changes in cigarette smoking are a more likely cause of the temporal trends than air pollution.

Changes in the demographics of smokers are another potential explanation. Over time, the poorer and less-educated segments of the population have become a progressively greater fraction of U.S. smokers (see Chapter 13, “Patterns of Tobacco Use Among U.S. Youth, Young Adults, and Adults”). Within birth cohorts, an increasing proportion of smokers come from population groups

characterized by less education and lower income and cessation rates are lower in these groups as well, compared with those having more education and higher incomes. Occupational and environmental exposures associated with increased lung cancer risk are also more common among those with less education and lower income. As a result, the effects of this demographic shift should be relatively uniform across cohorts, unlike the pattern observed in the figures. In addition, a demographic shift of this type in the characteristics of smokers would not affect rates of adenocarcinoma or squamous cell carcinoma or would not affect rates of adenocarcinoma or influence rates of squamous cell carcinoma.

In summary, adenocarcinoma has been increasing in the United States as a fraction of all lung cancers, becoming the most common histologic type of lung cancer. Despite decreases in smoking prevalence and concomitant decreases in squamous cell carcinoma, the incidence of lung adenocarcinoma among smokers has increased since the 1960s. Changes in the design and/or composition of cigarettes during the 1960s have increased the levels of tobacco-specific nitrosamines and other carcinogens in cigarette smoke. Evidence from birth-cohort models and epidemiologic studies are sufficient to conclude that the increased risk of lung adenocarcinoma among smokers is due to changes in the design and/or composition of cigarettes which increased the carcinogenicity of cigarette smoke.

Evidence for a Rising Risk of Adenocarcinoma of the Lung in the United States

Differences Across Time in Rates of Adenocarcinoma Within the United States and Across Countries

In a population, the principal determinants of risk for lung cancer are the prevalence of current smoking and the distribution of the duration of smoking among current and former smokers. As described previously, assessing the impact of differences in population-based smoking behaviors on rates of lung cancer is a complex undertaking. Even so, some understanding can be gained by comparing rates of lung cancer in countries where smokers have similar behaviors but smoke different types of cigarettes.

Incidence rates of adenocarcinoma of the lung and the proportions of adenocarcinoma in relation to all lung cancers increased in most countries through 1995–1997 (Devesa et al. 2005). These trends were particularly evident among women and reflected the higher risk of lung cancer accompanying their increasing smoking prevalence and a

rising proportion of lung cancer that was adenocarcinoma (Devesa et al. 2005). When examined at the national level, however, the rates of increase of adenocarcinoma and the patterns of the shift to adenocarcinoma as the most common form of lung cancer varied among countries (Devesa et al. 2005). In many countries—such as European countries (Devesa et al. 2005), including Italy (Russo et al. 1997); Japan (Yoshimi et al. 2003); and Hong Kong (Tse et al. 2009)—the patterns among men have roughly mimicked those of U.S. men, with falling rates of squamous cell carcinoma and initially rising but then falling rates of adenocarcinoma. Among women, interpretations of changes in rates of cancer by histologic type need to consider the rising rates of smoking prevalence for women. Regardless, rates of adenocarcinoma rose faster than rates of squamous cell carcinoma in most countries for which data were available (Devesa et al. 2005).

As described previously, flue-cured cigarettes of the type preferred in Australia, Canada, and the United Kingdom have substantially lower levels of tobacco-specific nitrosamines than do U.S.-style blended cigarettes and have higher levels of B[a]P (WHO 2008b). Tobacco-specific nitrosamines, specifically NNN and NNK, are organ-specific carcinogens for adenocarcinoma of the lung in animal models (IARC 2007; USDHHS 2010); NNK selectively induces adenocarcinoma of the lung in rats, mice, and hamsters. The level of NNAL, a metabolite of NNK, in the urine of smokers has been shown to be an independent predictor of risk for lung cancer even when the analysis controls for intensity (by cotinine concentration) and duration of smoking (Church et al. 2009; Yuan et al. 2009).

In terms of PAHs, one prospective cohort study found that a biomarker (phenanthrene tetraol) for PAH exposure was not an independent predictor of risk for lung cancer (Church et al. 2009). When the risk for lung cancer was examined by histologic type in this study, however, a significant association was found between NNAL in the urine and adenocarcinoma of the lung. The relationship between NNAL and risk for lung cancer was not significant for all other types of lung cancer combined, and the odds ratios for adenocarcinoma and other lung cancers did not differ significantly from each other (Church et al. 2009).

Mouth-level exposure to tobacco-specific nitrosamines in smoke has been examined among smokers in countries with high use of blended cigarettes (United States) and flue-cured unblended cigarettes (Australia, Canada, and the United Kingdom) (Ashley et al. 2010). Levels of NNK exposure among Australian and Canadian smokers were approximately one-third that of U.S. smokers, and levels of NNN exposure were 85–90% lower than the U.S. experience. Among smokers in the United

Kingdom, levels of NNK exposure were 20% lower than those of smokers in the United States, and levels of NNN were approximately 50% lower (Ashley et al. 2010).

In England and Scotland, flue-cured cigarettes remain popular, but measures of the level of exposure to tobacco-specific nitrosamines fall between those observed in smokers in the United States and in smokers in other countries where unblended cigarettes are common (Canada and Australia) (Ashley et al. 2010). In England (Bennett et al. 2008) and Scotland (Harkness et al. 2002), incidence rates of adenocarcinoma of the lung for men have increased only slightly, and squamous cell carcinoma remains the predominant lung cancer. Rates of squamous cell carcinoma among men in those countries are declining consistently as smoking prevalence drops.

In Canada, the incidence rate of adenocarcinoma among men in 1995–1997 remained lower than that of squamous cell carcinoma and well below the rate for White men in the United States (Figure 6.14) (Devesa et al. 2005). In contrast, rates for squamous cell carcinoma were similar for men in the United States and Canada in this period and in women as well (Devesa et al. 2005). Based on data up to 1997, the incidence of adenocarcinoma of the lung did not appear to be increasing over time in Canada. Instead, the data suggest that squamous cell carcinoma was decreasing so that adenocarcinoma represented an increasing fraction of lung cancers over time (Devesa et al. 2005).

In Australia, where flue-cured, unblended cigarettes with low tobacco-specific nitrosamine levels are also prominent, the rate of adenocarcinoma among men rose across birth cohorts and over time and exceeded the rates of squamous cell carcinoma for the most recent cohorts (Blizzard and Dwyer 2002). In contrast, the rate of adenocarcinoma among men in New South Wales, Australia, remained essentially constant between 1985 and 1997 (Figure 6.14) (Devesa et al. 2005) or rose only slightly over time. However, the rate for squamous cell carcinoma in 1995–1997 among New South Wales men declined to a level approximating that of adenocarcinoma (Figure 6.14) (Joshua et al. 2005). Similarly in South Australia, the rate of adenocarcinoma among men through 2000 was also relatively consistent over time, and the rate of squamous cell carcinoma fell to the same level as adenocarcinoma (Nguyen et al. 2003). However, in South Australia, the rate of adenocarcinoma increased among younger age groups.

When comparing the United States and Australia, the different patterns of cigarettes smoked may contribute to different patterns of lung cancer. Figure 6.15 presents gender- and age-specific rates of lung cancer mortality for the United States and Australia for 2000 (Peto et al. 2006). Lung cancer death rates were lower in all age groups for

men and women in Australia compared with the United States. Detailed comparisons of smoking behaviors similar to those used to model U.S. death rates are not available for Australia, but estimates of the prevalence of smoking show a general similarity for Australia and the United States, particularly during the 1990s (White et al. 2003).

Figure 6.16 presents information on adenocarcinoma as a proportion of all lung cancers with a designated histologic type, by birth cohort and gender for the United States and Australia (Burns et al. 2011a). In Australia, a modest rise occurs in the proportion of lung cancers that are adenocarcinoma across the birth cohorts for both genders, but the fraction remains well below 50% for men and only slightly above 50% for women. Data for the United States show a much more dramatic increase in the proportion of lung cancer that is adenocarcinoma, with the proportion exceeding 60% in the most recent cohorts for White men and women. Notably, the earliest birth cohorts for the U.S. population, those born from 1880–1900, have proportions similar to those found in Australia.

In summary, rates for squamous cell carcinoma of the lung have been decreasing in most countries in which the prevalence of smoking has been declining. In contrast, the incidence rate of adenocarcinoma has been rising in the United States and has been level or increasing in other countries, with the general result that adenocarcinoma has increased as a proportion of lung cancer in most countries. The magnitude of that increase has differed between the United States, where the predominant type of cigarette is made of blended tobacco with relatively high levels of tobacco-specific nitrosamines, and Canada and Australia, where flue-cured cigarettes with lower levels of tobacco-specific nitrosamines predominate. Incidence rates of adenocarcinoma and the proportion of lung cancer that is adenocarcinoma are substantially higher in the United States than in Canada and Australia.

Effects of Filter Ventilation on Deposition of Smoke in the Lung and the Toxicity of This Smoke

One potential explanation for the rise in adenocarcinoma of the lung in the United States is a change in the pattern of smoking after ventilated filters were introduced to lower the machine-measured yields of tar and nicotine (Zheng et al. 1994; Thun et al. 1997a; Wingo et al. 1999). Smokers who shift to brands with nominally lower machine-measured yields with ventilated filters change their smoking pattern to restore their nicotine delivery to the level needed to sustain their addiction. As described previously, changes include increasing puff volume and velocity, greater duration of puffing, and shortening the

Figure 6.14 Trends in incidence rates for lung cancer (age adjusted, world standard), by histologic type (squamous cell carcinoma, small cell carcinoma, and adenocarcinoma) and geographic area, 1980–1982 to 1995–1997

A. Squamous cell carcinoma of the lung

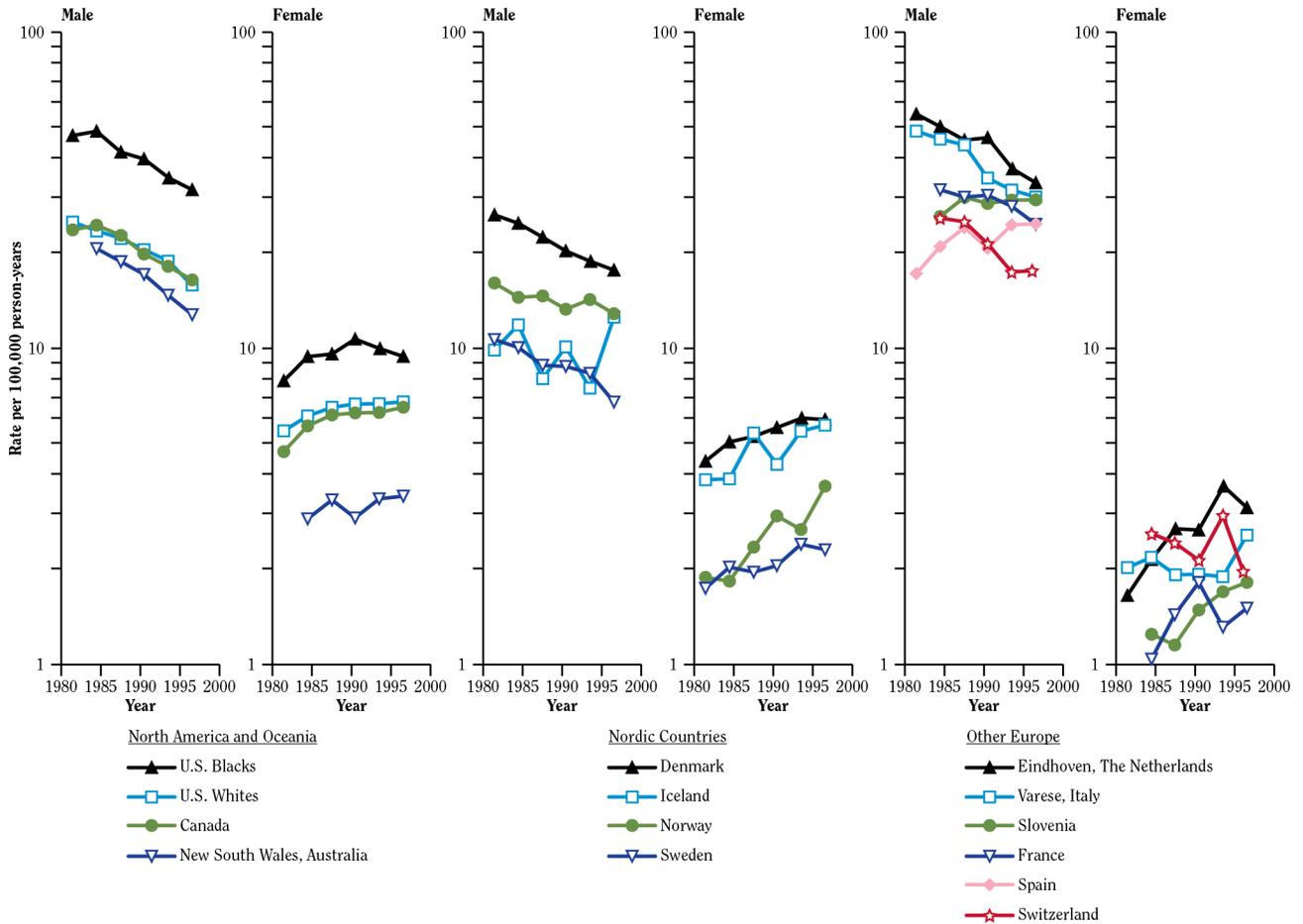


Figure 6.14 Continued

B. Small cell carcinoma of the lung

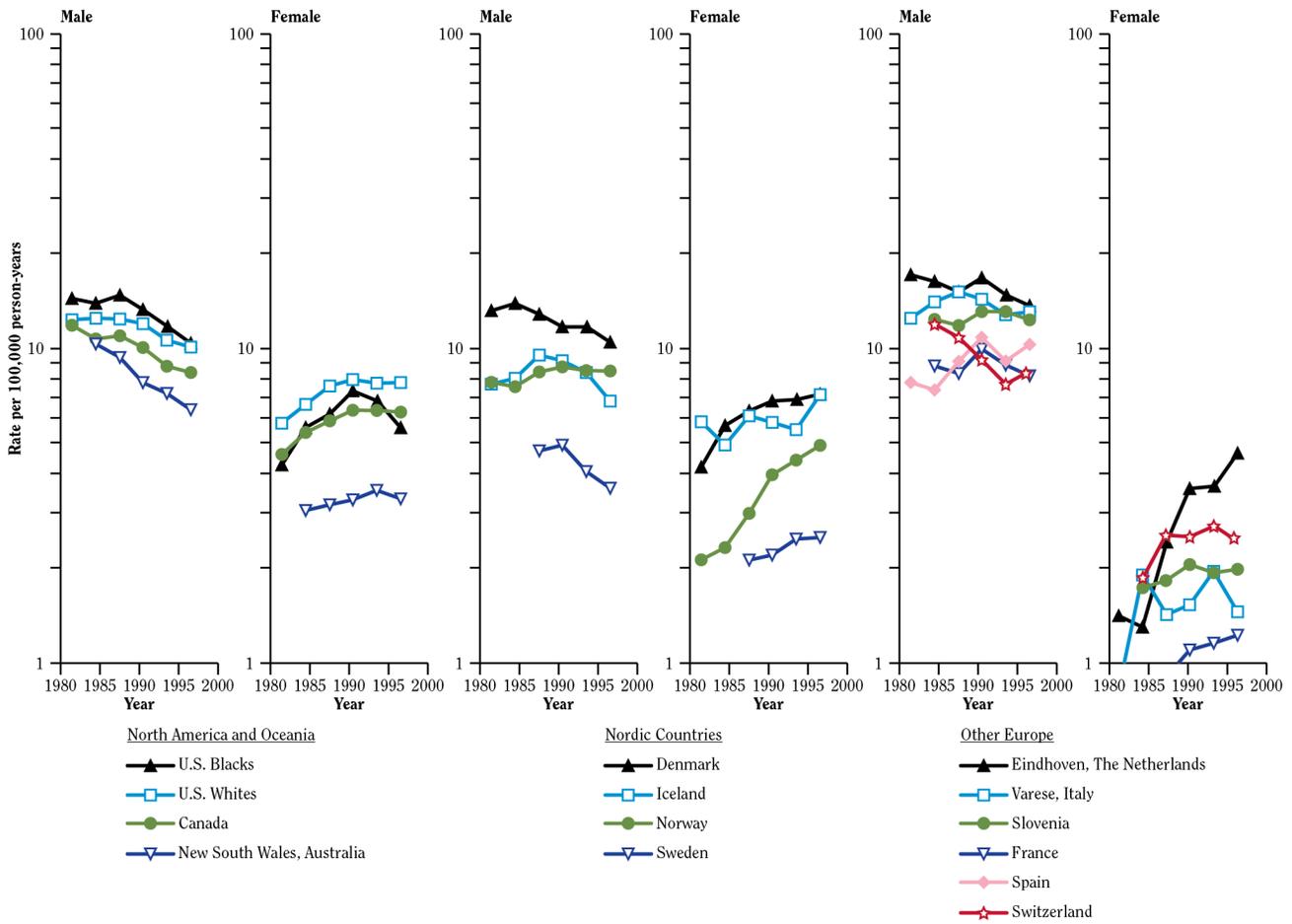
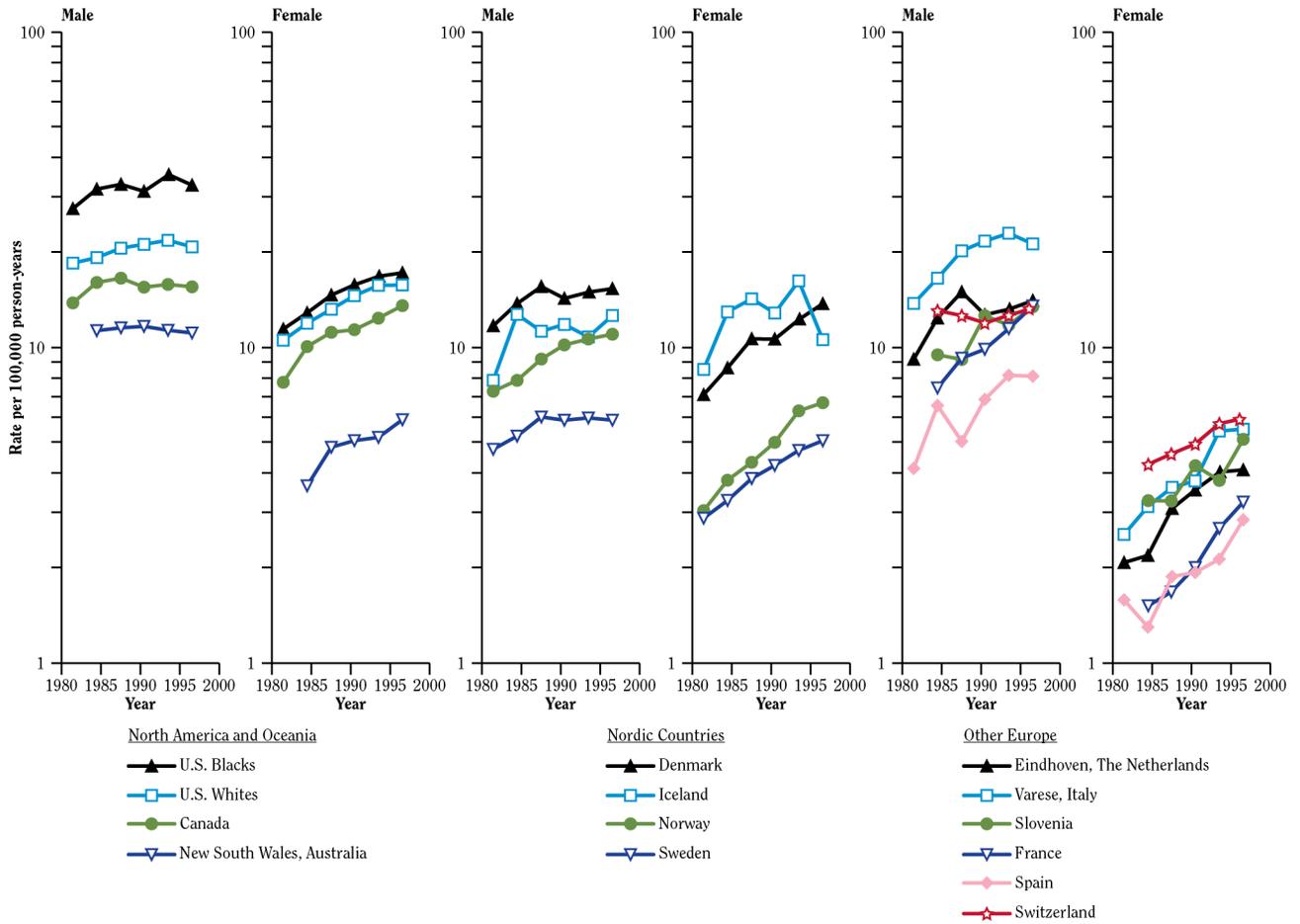


Figure 6.14 Continued

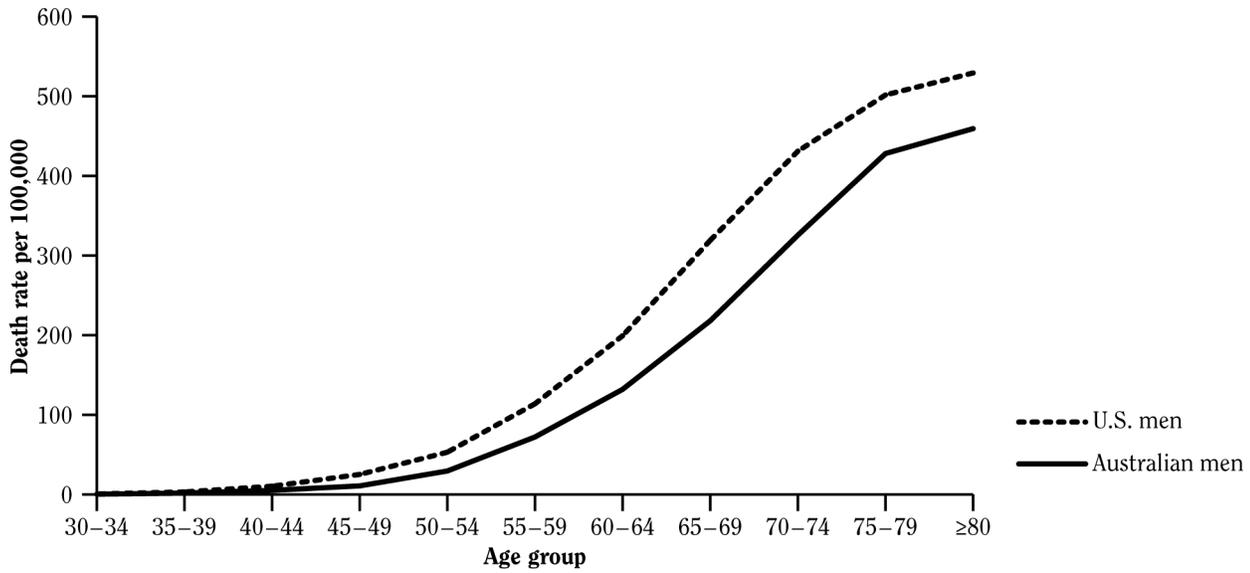
C. Adenocarcinoma of the lung



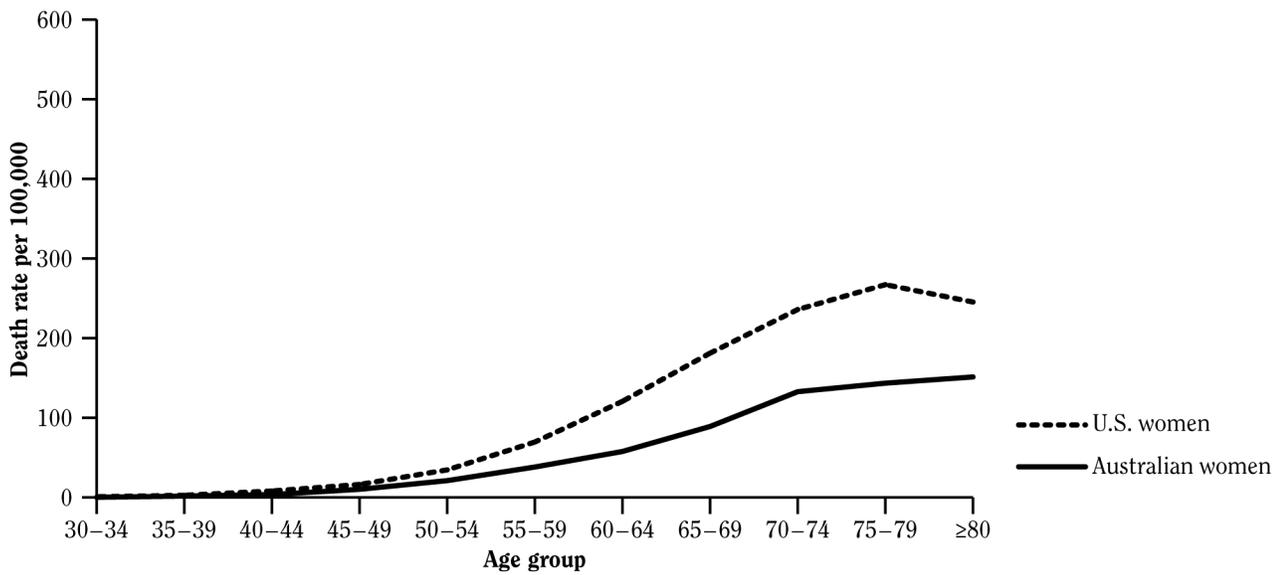
Source: Devesa et al. 2005. Reprinted with permission from John Wiley & Sons, Inc., © 2005.
 Note: Incidence rates were calculated for 3-year time periods: 1980–1982 (plotted at 1981.5), 1983–1985 (plotted at 1984.5), 1986–1988 (plotted at 1987.5), 1989–1991 (plotted at 1990.5), 1992–1994 (plotted at 1993.5), 1996 (Switzerland only; plotted at 1996), and 1995–1997 (plotted at 1996.5). Incidence rates were age-adjusted by the direct method, using the Segi world standard (Bray et al. 2002), and expressed per 100,000 person-years.

Figure 6.15 Age-specific rates of lung cancer death, by gender and age group, in the United States and Australia, 2000

A. Men



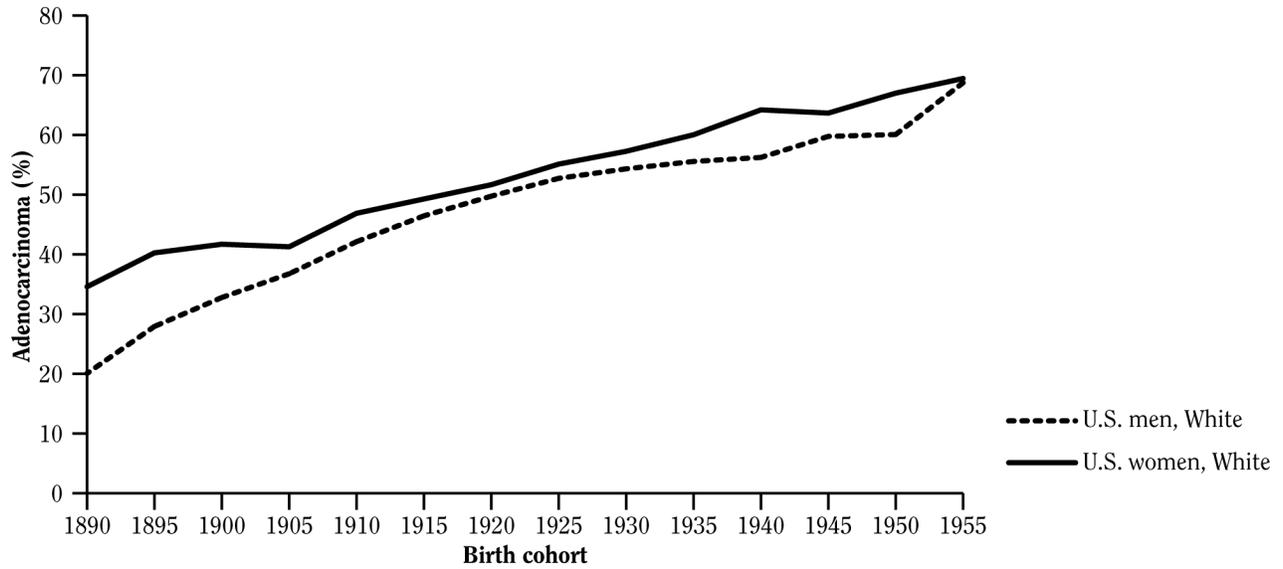
B. Women



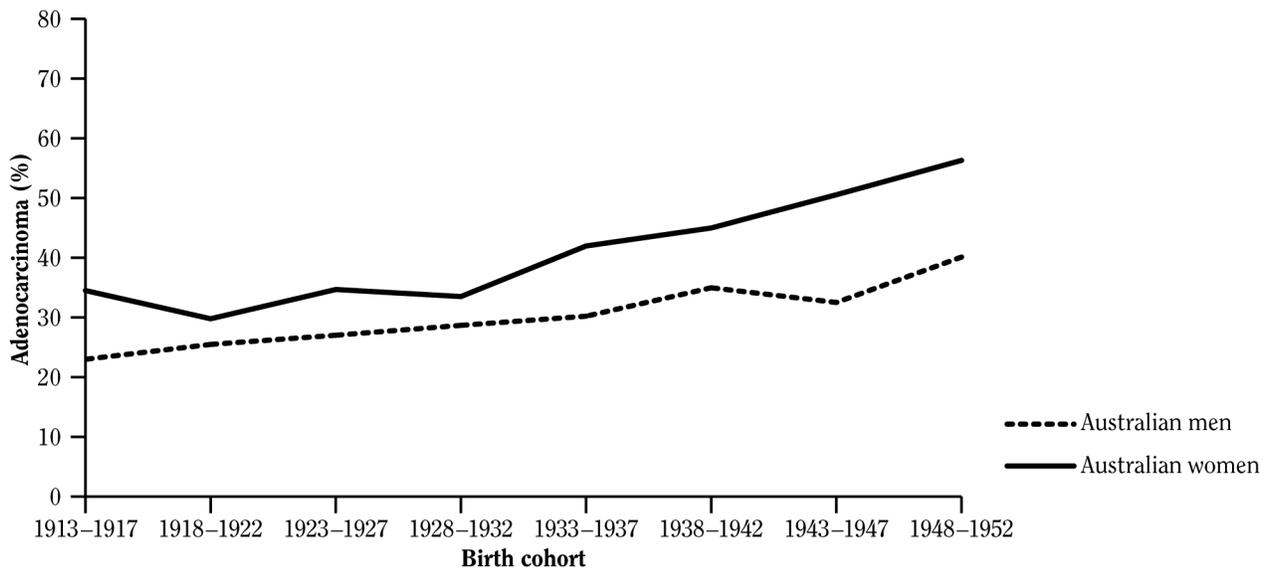
Source: Peto et al. 2006.

Figure 6.16 Adenocarcinoma as a percentage of designated lung cancers in U.S. White men and women and Australian men and women, by various birth cohorts, 1890–1955

A. U.S. White men and women



B. Australian men and women



Source: Burns et al. 2011a. Reprinted with permission from Science & Business Media B.V., © 2011.

Note: Data for the Australian national cancer registry provided by Helen Farrugia, Director Information Systems, Cancer Epidemiology Centre, The Cancer Council Victoria.

intervals between puffs (NCI 2001). In addition, smokers may increase the depth of inhalation and hold the smoke in their lungs longer to increase nicotine uptake. Notably, there is little difference in markers of nicotine ingestion between smokers of brands of cigarettes with substantially different machine yields (Jarvis et al. 2001; NCI 2001). Increasing depth of inhalation and other more intense smoking patterns likely increase the deposition of smoke in the alveolar region of the lung.

Most physical models of particles disseminating in the lung incorporate the size-dependence of particle deposition in the lung, but do not fully reflect the complexity of smoking behavior. As a consequence, the models may underestimate the fraction of smoke particles retained in the lung (Stratton et al. 2001; Gower and Hammond 2007; Rostami 2009), raising questions about their validity in characterizing the distribution and deposition of particles in different regions of the lung with different tobacco products. An analysis by Gower and Hammond (2007) of models of cigarette smoke deposition that examined the effects of the changes in pattern of smoking after a shift to brands with lower machine-measured yields showed that puff time, inhalation depth, time holding one's breath, and exhalation time may affect total smoke deposition. While a shift in deposition to the alveolar level remains a possibility, the researchers could not determine whether the changes in patterns of smoking resulting from the use of more highly ventilated cigarettes could produce a large enough shift in the location of deposition to change the pattern of incidence of a specific histologic type of lung cancer. Although the magnitude of the potential change in regional deposition in the lung remains uncertain, existing evidence suggests that changes in the pattern of smoking, with a shift to lower tar-yield cigarettes, will likely increase the fraction of cigarette smoke particles deposited in the alveolar region of the lung. This shift may also have played a role in increasing the risk of adenocarcinoma of the lung over time.

The introduction of ventilated filters, or changes in the design and composition of cigarettes that accompanied their introduction, may have increased the carcinogenicity of cigarette smoke. Given the dilution of smoke by filter ventilation and the compensation for that dilution by smokers when these cigarettes are used, comparisons of the toxicity of cigarettes on a per-cigarette basis can be misleading, making comparisons on the basis of "per mg tar" or "per mg total particulate matter" more useful.

The level of filter ventilation alters the composition of tobacco smoke. In general, based on the International Organization for Standardization protocol and under more intense smoking parameters, higher levels of ventilation result in more complete combustion in

flue-cured, unblended cigarettes smoked by a machine (Adam et al. 2010). When experimental (Rickert et al. 2007) or commercial (Roemer et al. 2004) U.S.-blended cigarettes were compared with experimental, unblended, flue-cured cigarettes (Monitor-7 Canadian reference cigarette) in mutagenicity testing, the level of revertants per mg (the indicator of mutational strength) of the total particulate matter was lower for the unblended Canadian reference cigarette. For Kentucky reference cigarettes, mutagenicity per mg of total particulate matter was 30–40% lower for unfiltered cigarettes than for the same cigarette with a filter added (Shin et al. 2009).

Tobacco industry documents show internal company research demonstrating that increasing filter ventilation increases the mutagenicity of the resultant tar on a per-mg of tar basis (Johnson et al. 2009). The published evidence produced by the industry is less clear. In a study from R.J. Reynolds, Chepiga and colleagues (2000) compared full-flavor, full-flavor low-tar, and ultralow-tar cigarettes and reported a nonsignificant trend of increased revertants per mg of tar in mutagenicity studies as the level of machine-measured tar decreased. In a study from Philip Morris, Roemer and colleagues (2004) reported that higher total yields of particulate matter were associated with a trend toward less mutagenic activity per mg of total particulate matter. In another study from Philip Morris, Patskan and colleagues (2008) compared the mutagenic activity of Marlboro full flavor, Marlboro Lights, and Marlboro Ultra Lights, finding that mutagenic activity was higher per mg of total particulate matter for Marlboro Ultra Lights, but this was for only some *Salmonella* strains used in the mutagenicity testing and for only some runs. Thus, the evidence supports a modest increase in the mutagenicity of tobacco tar as the level of machine-measured tar falls; this effect may result from increased ventilation.

These data should be interpreted with caution for several reasons. Mutagenicity is generally used as only a screening test, is often poorly associated with carcinogenicity in humans, and has not been quantitatively associated with differences in human risk. In addition, most of the studies described previously compared smoke generated under standardized machine-testing protocols. In actual use, smokers change their patterns of smoking, compensating for the design changes that result in lower yields of machine-measured tar and nicotine. This compensatory smoking behavior makes comparisons of cigarettes with very different machine-tested yields difficult to interpret relative to carcinogenicity in humans when the smoke for the different cigarettes is generated using a single, standardized, machine-smoking protocol.

Existing evidence about changes in the patterns of smoking cigarettes with low yields of tar and high ventilation supports a shift in the deposition of smoke in the lung toward the alveolar region; this shift likely contributes to the observed increase in adenocarcinoma of the lung. Research has not clarified whether the magnitude of this shift in lung deposition, by itself, is great enough to explain the dramatic increase in adenocarcinoma observed in the United States. The mutagenicity of tobacco tar from cigarettes with lower yields of machine-measured tar is trending upward. However, the trend is modest in size, and difficulties in extrapolating results from mutagenicity testing to risk for humans make it difficult to know whether these changes contribute to increasing the risk of lung cancer.

Evidence Synthesis

The design and composition of cigarettes have changed substantively since the first major wave of evidence linking smoking to lung cancer in the 1950s. Although the details of these changes are only partially understood, changes in design—notably the addition of ventilated filters—have clearly changed the pattern of smoking, including more intense puffing. In addition, changes in the composition of cigarettes have resulted in incompletely characterized alterations in the chemical composition of cigarette smoke. Documented changes include increases in tobacco-specific nitrosamines and decreases in PAHs in the smoke of U.S. cigarettes. Substantial differences between U.S. cigarettes and those of many other nations include the use of blended tobacco in U.S. cigarettes and the use of unblended, flue-cured tobacco in cigarettes in Australia, Canada, and the United Kingdom. The United States has somewhat preceded most other developed countries in the adoption of filtered and low-yield, machine-tested cigarettes, but U.S. products are also used widely in most countries. These changes raise a question of whether rates of lung cancer have been altered by the changes in the design and composition of cigarettes—changes that were accompanied by an initial belief that lower yields of machine-tested tar might signal a lower risk for lung cancer. In fact, the risk of lung cancer in the United States may have increased as a result of such changes.

Comparison of results of CPS-I and CPS-II—two large epidemiologic studies conducted 20 years apart by ACS—demonstrated an increased risk of death from lung cancer from smoking across the 20-year interval between the studies. For female smokers, the results from the

contemporary cohorts show that lung cancer risk continued to rise through 2000–2010. Modeling of risks of lung cancer from smoking behaviors suggests that risk estimates based on the smoking experience in the 1960s underestimated the current incidence of lung cancer. In addition, the incidence of adenocarcinoma of the lung and the proportion of lung cancer that is adenocarcinoma has increased dramatically during the past several decades. This shift from squamous cell carcinoma to adenocarcinoma is confined to smokers, because neither the overall risk of lung cancer nor the risk of adenocarcinoma has changed over time among never smokers. The rate of squamous cell carcinoma of the lung has declined in the United States since the 1980s and is well-predicted by declines in smoking behaviors, but the rate of adenocarcinoma continued to rise for an additional 10–15 years before either leveling off or beginning to decline. Birth-cohort-specific analyses of trends in overall mortality from lung cancer and the incidence of type-specific lung cancer suggest that increases in diagnostic accuracy, differences by tumor type in the time course of excess risk reduction with cessation, and underestimation of the effect of intensity and duration of smoking in the studies that defined risk in the 1960s do not explain the observed trends. In contrast, a change in the risk of the cigarettes smoked over time does explain the increase in risk. A shift in the demographic composition of smokers toward those groups with less income and education may contribute to the increased risk of lung cancer among smokers, but this shift does not likely explain the increase in adenocarcinoma or the difference in the rates of incidence of squamous cell carcinoma and adenocarcinoma.

Most countries have experienced increases in the proportion of all lung cancer that is adenocarcinoma, but substantial differences are found in the extent of this increase when comparing the United States, where blended cigarettes are used, with Australia and Canada, where unblended cigarettes are used. Adenocarcinoma in the United States has increased more steeply, represents a much higher fraction of lung cancer, and has higher absolute incidence rates than those of Australia or Canada. Compared with unblended cigarettes, U.S.-style blended cigarettes have dramatically higher levels of tobacco-specific nitrosamines—an organ-specific carcinogen of adenocarcinoma of the lung in animals. Exposure to tobacco-specific nitrosamines is also much higher among U.S. smokers than among their counterparts in Australia and Canada. Levels of a metabolite of NNK, a tobacco-specific nitrosamine, are an independent risk predictor for the occurrence of lung cancer after controlling for the intensity and duration of smoking.

Compensatory changes in the patterns of puffing and inhaling smoke by smokers switching to cigarettes with low yields of toxicants may increase the deposition of smoke particles in the alveolar region of the lung. This is supported by modeling of particle deposition in the lung that suggests this effect likely increases the deposition of particles in the alveolar region. Increased alveolar deposition and increasing tobacco-specific nitrosamine levels over time may have combined to increase the risk for adenocarcinoma.

Conclusions

1. The evidence is sufficient to conclude that the risk of developing adenocarcinoma of the lung from cigarette smoking has increased since the 1960s.
2. The evidence is sufficient to conclude that the increased risk of adenocarcinoma of the lung in smokers results from changes in the design and composition of cigarettes since the 1950s.
3. The evidence is not sufficient to specify which design changes are responsible for the increased risk of adenocarcinoma, but there is suggestive evidence that ventilated filters and increased levels of tobacco-specific nitrosamines have played a role.
4. The evidence shows that the decline of squamous cell carcinoma follows the trend of declining smoking prevalence.

Implications

The evidence presented has multiple implications. Above all, if the risk of lung cancer has increased with changes in the design and composition of cigarettes, then the potential exists to reverse that increase in risk through changes in design and composition. Even a mod-

est reduction in the large burden of mortality from lung cancer would result in saving substantial numbers of lives over time.

The evidence reviewed suggests that differences in the design and composition of cigarettes may contribute to differences in smoking-related risks of lung cancer in different populations and different geographic locations. Data also suggest that epidemiologic studies treating all cigarettes as having identical risks, or using single biomarkers of exposure to quantify actual exposure to the multiple carcinogens in cigarette smoke, should be undertaken with some caution. The number of cigarettes smoked per day, measures of cotinine in biologic samples, and other measures of total smoke exposure will remain useful for estimating total smoke exposure and population risk. However, the potential for differences in products to yield differences in risk suggests that a broader array of biomarkers of exposure should be used to examine whether differences in the toxicity and composition of a given total exposure to smoke may also play an important role in determining differences in risks.

The changing risk for lung cancer associated with cigarettes over time also has implications for the surveillance of tobacco products. Monitoring tobacco products needs to go beyond tracking the most obvious changes, such as the addition of a filter, to assess the characteristics of the tobacco in the cigarette, how the product is manufactured, how it is likely to be smoked, the design of the cigarette, and its performance under a variety of smoking patterns. The absence of such information for past and current tobacco products limits the ability to more fully study the effects of changes in the design and composition of cigarettes on risks of disease. The availability of such information could help in the assessment of potential differences in risks going forward.

Finally, the rise in the risk of adenocarcinoma of the lung from smoking was unanticipated. This experience, like that of cigarettes with purportedly low yields of toxicants, indicates that changes to cigarettes should undergo careful, evidence-based assessments as such changes are being considered.

Liver Cancer

In many parts of the world, liver cancer remains a leading cause of cancer mortality. Primary liver cancer, the great majority of which is hepatocellular carcinoma (HCC), generally presents at an advanced stage with limited treatment options and a poor prognosis. Although worldwide liver cancer is the sixth most common cancer in terms of incidence, it represents the third most common cause of cancer-related death (Ferlay et al. 2010).

A number of strong risk factors for HCC have been identified, including infection with the hepatitis B or C viruses (HBV, HCV), exposure to aflatoxins, and alcohol-associated cirrhosis (London and McGlynn 2006). The incidence of liver cancer varies geographically worldwide, with rates generally consistent with the regional prevalence of the primary viral etiologic factors (Nordenstedt et al. 2010). Globally, Asia and sub-Saharan Africa—with endemic HBV infection and common dietary exposure to aflatoxins—have the highest incidence of HCC. Rates of HCC appear to have stabilized or started to decline in several Asian countries, where widespread vaccination against HBV and reduction of HBV cofactors have occurred during the past few decades (Yuen et al. 2009). HCV infection has been the primary etiologic agent for HCC in various countries having substantial incidence of HCC (London and McGlynn 2006).

Historically, the United States has had a low incidence of liver cancer and low death rates for the disease. However, rates of HCC have been increasing in the United States over the last two decades (Altekruse et al. 2009; El-Serag 2011). In recent years, Whites and Blacks, particularly those 50–59 years of age, have experienced the largest annual percentage increases in rates of HCC; rates of HCC among Asians/Pacific Islanders have been stable (O'Connor et al. 2010). The increased rates of HCC in the United States appear to be largely a consequence of chronic HCV infection (El-Serag 2004). However, obesity, diabetes, and associated nonalcoholic fatty liver disease, and the substantial burden of chronic HBV infection among foreign-born Asians may also be potential contributors to the increasing incidence of HCC (Larsson and Wolk 2007; Starley et al. 2010). In addition to viral hepatitis, cirrhosis from consumption of alcohol represents an important cause of HCC worldwide (London and McGlynn 2006). HCC is more common among men than women, which likely reflects gender differences in exposure to viral hepatitis and rates of progression of that

disease, differences in smoking and in consumption of alcohol, and perhaps hormonal differences.

The association between smoking and HCC is complicated by the potential for confounding with the causal factors of consumption of alcohol and HBV and HCV infection. For example, people who drink alcohol are more likely to be smokers than people who do not drink alcohol (Dawson 2000). In addition, most HCV infections worldwide are acquired by injecting drugs, and the prevalence of smoking is very high among injection drug users (Marshall et al. 2011). In regions of the world with a high incidence of HCC, HBV infection is generally acquired perinatally or during early childhood. However, in other regions, HBV may be more commonly acquired through parenteral or sexual transmission; these behaviors may also be associated with smoking. Hence, the potential confounders must be examined carefully when assessing the association between smoking and HCC. However, considerable epidemiologic evidence, including data from studies in which measures have been taken to address potential confounding, indicates that smokers are at an increased risk for liver cancer (IARC 2004).

Conclusions of Previous Surgeon General's Reports

The Surgeon General's report on smoking cessation (USDHHS 1990) noted an association between smoking and HCC that persisted after controlling for potentially confounding lifestyle factors, including consumption of alcohol. The report also noted that HBV infections may modify the effects of smoking on the risk of liver cancer. The Surgeon General's report on women and smoking (USDHHS 2001) concluded that smoking may be a contributing factor to the development of liver cancer. The Surgeon General's report on the health consequences of smoking (USDHHS 2004) noted a consistent association between smoking and HCC after controlling for potentially confounding factors, but it called for further consideration of the history of viral hepatitis and consumption of alcohol. Overall, the 2004 report concluded that although the data were suggestive of an association between smoking and liver cancer, further evidence was required to classify smoking as a cause of liver cancer.

Biologic Basis

Circulating carcinogens from tobacco smoke are metabolized in the liver, exposing the liver to many absorbed carcinogens. Experimental studies have identified several constituents of tobacco smoke (e.g., *N*-nitrosodimethylamine, 4-aminobiphenyl) as liver carcinogens (IARC 2004). Limited human data on smoke-related carcinogens have suggested increased levels of 4-aminobiphenyl and PAH adducts in HCC tissues compared with normal liver tissues (Wang et al. 1998; Chen et al. 2002). Therefore, long-term exposure to carcinogens in smoke may lead to cellular damage in the liver and contribute to the development of cancer. Cigarette smoking may also contribute to liver carcinogenesis through the development of liver fibrosis (Dev et al. 2006; Mallat et al. 2008; Altamirano and Bataller 2010). Similar to their effects on other fibrogenic conditions (e.g., cardiac, renal, or pancreatic diseases), components of smoke may induce pro-inflammatory cytokines, oxidative stress pathways, and direct fibrogenic mediators (e.g., transforming growth factor- β 1, angiotensin II) (Altamirano and Bataller 2010). Smoking has also been recognized as a risk factor for primary biliary cirrhosis, which itself can progress to HCC (Zein et al. 2006; Corpechot et al. 2012; Smyk et al. 2012). Although their results have been inconsistent, several epidemiologic studies have demonstrated that smoking substantially increases the risk for progression from chronic liver disease to HCC (Tsukuma et al. 1993; Marrero et al. 2005; Fujita et al. 2006). Further clarification is needed of the mechanistic and epidemiologic effects of smoking in relation to potential etiologic agents that can influence these pathways (chronic inflammation and/or oxidative stress associated with HCV infection, obesity, or diabetes).

Epidemiologic Evidence

Since the 2004 report of the Surgeon General, 90 additional studies have been published or identified that report on the association between smoking and liver cancer. IARC (2004) concluded that there was sufficient evidence of a causal association between cigarette smoking and liver cancer. Subsequently, Lee and colleagues (2009) published a meta-analysis that was based on the studies considered in the 2004 IARC report.

Studies for the current review were compiled by searching the MEDLINE database (from January 1966 to December 2012) using the medical subject headings “tobacco,” “smoking,” “liver neoplasms,” or “hepatocellular carcinoma” and by examining references cited in

the previous Surgeon General’s reports, the IARC (2004) monograph on smoking and liver cancer, and the associated meta-analysis (Lee et al. 2009). The epidemiologic data came from a wide range of studies in both low- and high-incidence countries (Tables 6.3S and 6.4S). For many studies, the outcome was defined as HCC and was based on clinical, radiographic, laboratory (alpha-fetoprotein levels), or pathologic criteria. A minority of studies relied on linkage to cancer or mortality registries, often using primary liver cancer as the outcome defined by the coding of cancer diagnoses from the *International Classification of Disease for Oncology* or causes of death from the *International Classification of Diseases*. Some studies were unable to distinguish between HCC and intrahepatic cholangiocarcinoma; however, none of these studies were from geographic regions where intrahepatic cholangiocarcinoma would likely represent a substantial portion of primary liver cancers. Studies that did not explicitly differentiate between primary and secondary liver cancer (and therefore may have included cancers with a different primary site that had metastasized to the liver) were excluded from the analysis. Quantitative analyses included all studies that reported sufficient information to abstract or calculate an effect estimate and 95% confidence interval (CI); these analyses were stratified by study design (case-control or cohort).

This review focused on evaluations of the separate effects observed in current smokers, ever smokers, and former smokers in comparisons with never smokers or nonsmokers; studies with a reference group other than never smokers or nonsmokers were excluded (e.g., those comparing heavy smokers with light smokers). The quantitative analyses excluded all studies that compared liver cancer cases with controls who had chronic viral hepatitis, cirrhosis, or other chronic liver disease. Finally, the review separately examined the effects of smoking on HCC in studies that controlled for confounding by the main etiologic factors (HBV, HCV, and consumption of alcohol) for HCC in the region under study. Assessment of viral hepatitis status was considered adequate for inclusion in the quantitative analysis if the study reported on serological measurement of HBV surface antigen (HBsAg) or antibodies to HCV (anti-HCV) as indicators of chronic HBV or HCV infection, respectively.

Overall, 113 studies—including 59 case-control (Table 6.3S) and 54 cohort studies (Table 6.4S)—provided data on smoking and primary liver cancer. These studies, taken together, offered substantial heterogeneity in design, study population, assessment of smoking exposure, and the reporting of risk estimates. Many studies, however, were limited by having few HCC cases and reported nonsignificant increases in risk associated with

various measures of smoking. Furthermore, many studies did not adequately control for potential confounding by major causal factors such as consumption of alcohol or HBV or HCV infection.

In an analysis combining data from 31 studies (12 case-control and 19 cohort) that reported sufficient information to estimate risk for HCC in current smokers compared with nonsmokers (Figure 6.17), the overall estimate for RR was 1.7 (95% CI, 1.5–1.9). The relationship between current smoking and HCC was similar in cohort studies (overall RR = 1.7; 95% CI, 1.5–1.9) and case-control studies (RR = 1.6; 95% CI, 1.2–2.1). When 11 studies (6 case-control and 5 cohort) that controlled for confounding by the primary etiologic factors (e.g., HBV, HCV, consumption of alcohol) were analyzed (Figure 6.18), the RR (1.6; 95% CI, 1.2–2.0) was similar to that in the overall analysis. Among these studies that directly addressed confounding, the relationship between current smoking and HCC was stronger in cohort studies (RR = 2.2; 95% CI, 1.4–3.3) than in case-control studies (odds ratio [OR] = 1.2; 95% CI, 0.9–1.5). Overall, these findings are similar to those in the meta-analysis performed by Lee and colleagues (2009) in association with the 2004 IARC report, which reported a 51% increased risk for liver cancer for current smokers compared with never smokers (meta-RR = 1.51; 95% CI, 1.37–1.67). The findings of the IARC (2004) review and the current review are similar, except that the present review includes a greater number of studies (31 vs. 20) and includes studies that reported results for only one gender. Both the present review and the IARC analysis defined current smoking as reported at entry into the cohort or at the time of diagnosis of liver cancer.

Among 26 studies (18 case-control and 8 cohort) with evaluable comparisons between ever smokers and never smokers (Figure 6.19), the risk for HCC was increased among ever smokers (RR = 1.4; 95% CI, 1.3–1.6), with comparable estimates of the magnitude of effect observed in case-control studies (RR = 1.4; 95% CI, 1.1–1.7) and cohort studies (RR = 1.5; 95% CI, 1.3–1.7). In the 4 studies that adjusted for exposure to the primary etiologic agents (Figure 6.20), the magnitude of risk was notably higher among ever smokers (RR = 1.7; 95% CI, 1.4–2.2) compared to the magnitude of risk among ever smokers in studies (Figure 6.19).

Among 33 case-control studies that evaluated dose-response relationships between smoking (e.g., increasing intensity, pack-years, or duration) and HCC, only 6 (18%) reported a statistically significant trend. Among 26 cohort studies that evaluated these relationships, 10 (38%) reported a significant dose-response effect of smoking intensity on increased risk for HCC, and 2 (8%) reported an inverse dose-response relationship. Many studies that

evaluated dose response did not formally test for trends; however, a substantial proportion of these studies were not adequately powered to address such relationships. In their meta-analysis, Lee and colleagues (2009) summarized data from 7 studies with evaluable estimates and reported a significant dose-response trend showing increased risk for liver cancer with higher number of cigarettes smoked. However, this effect was notably less apparent among case-control studies that used hospital-based instead of population-based control groups.

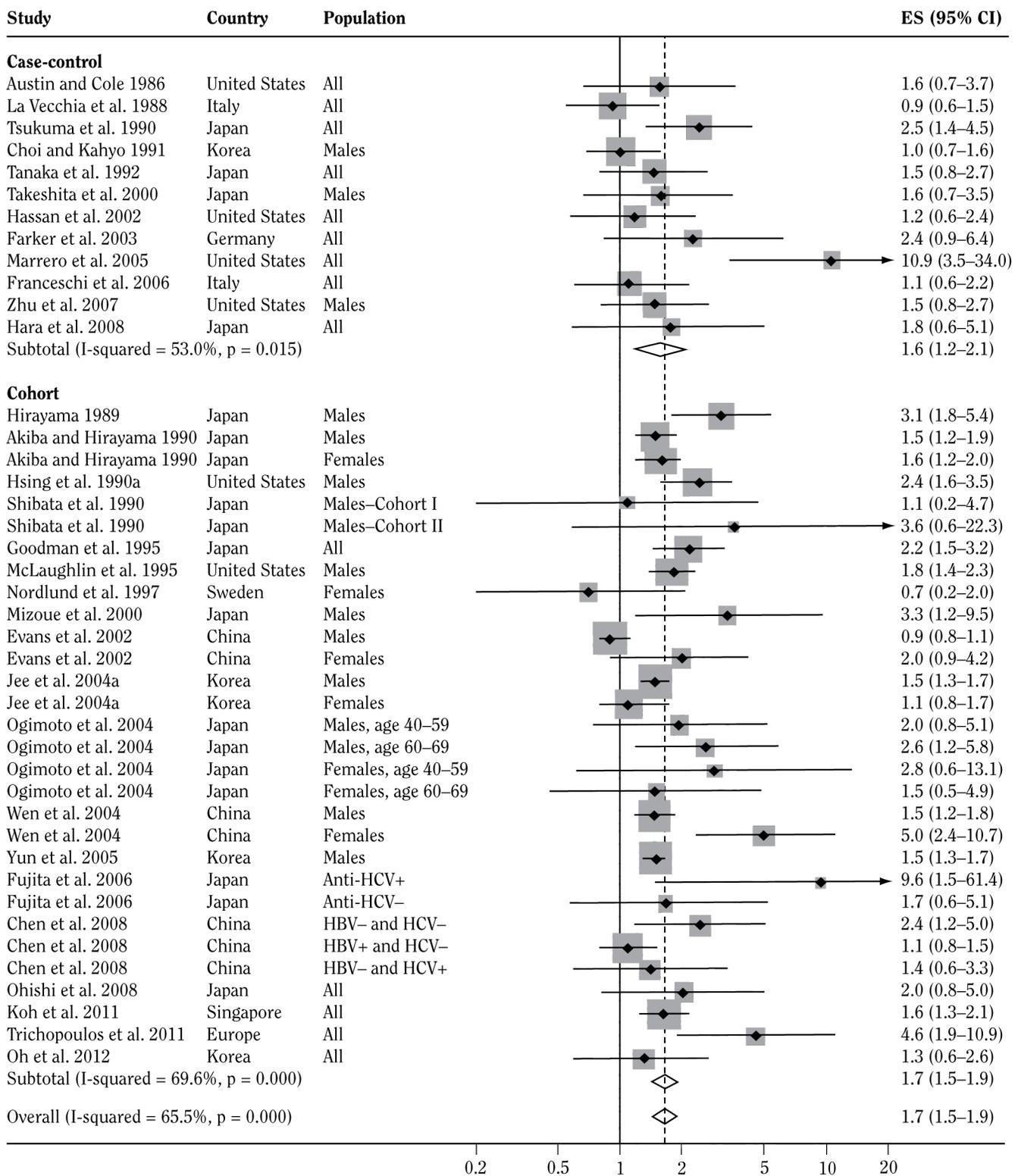
Because of concern for residual confounding of smoking effects by coinfection with viral hepatitis, the association between smoking and HCC was evaluated in the present review among persons who did not have evidence for chronic viral hepatitis. In an analysis combining data from 13 studies (9 case-control and 4 cohort) that estimated risk among persons who were negative for markers of chronic HBV or HCV infection (Figure 6.21), the risk of HCC among current or ever smokers was significantly increased (RR = 1.8; 95% CI, 1.2–2.7) in a comparison with never smokers. After excluding a study that reported markedly increased risk among persons who were negative for HBV and HCV (Jeng et al. 2009), the estimated risk was attenuated but still significant (RR = 1.3; 95% CI, 1.0–1.8). Finally, when the analysis was restricted to the 3 studies that included only persons negative for both HBsAg and anti-HCV and also adjusted for consumption of alcohol (Kuper et al. 2000; Yuan et al. 2004; Koh et al. 2011), the RR was 1.7 (95% CI, 1.2–2.5).

The present review did not identify any studies that directly evaluated the effects of interventions aimed at smoking cessation on subsequent risk for liver cancer. Among 23 studies with the requisite data available from the publication (11 case-control and 12 cohort) (Figure 6.22), the risk for liver cancer among persons identified as former smokers relative to never smokers was lower (RR = 1.4; 95% CI, 1.1–1.7) than for current smokers (RR = 1.7, 95% CI 1.5–1.9).

Despite substantial geographic variation in the incidence of HCC and the distribution of etiologic factors, smoking was consistently related to increased risk for HCC in all geographic regions, although the magnitude of the association was not as strong in studies conducted in European countries. Among 35 studies conducted in Asian countries (Table 6.3S), the RR for HCC among current or ever smokers was 1.5 (95% CI, 1.4–1.6).

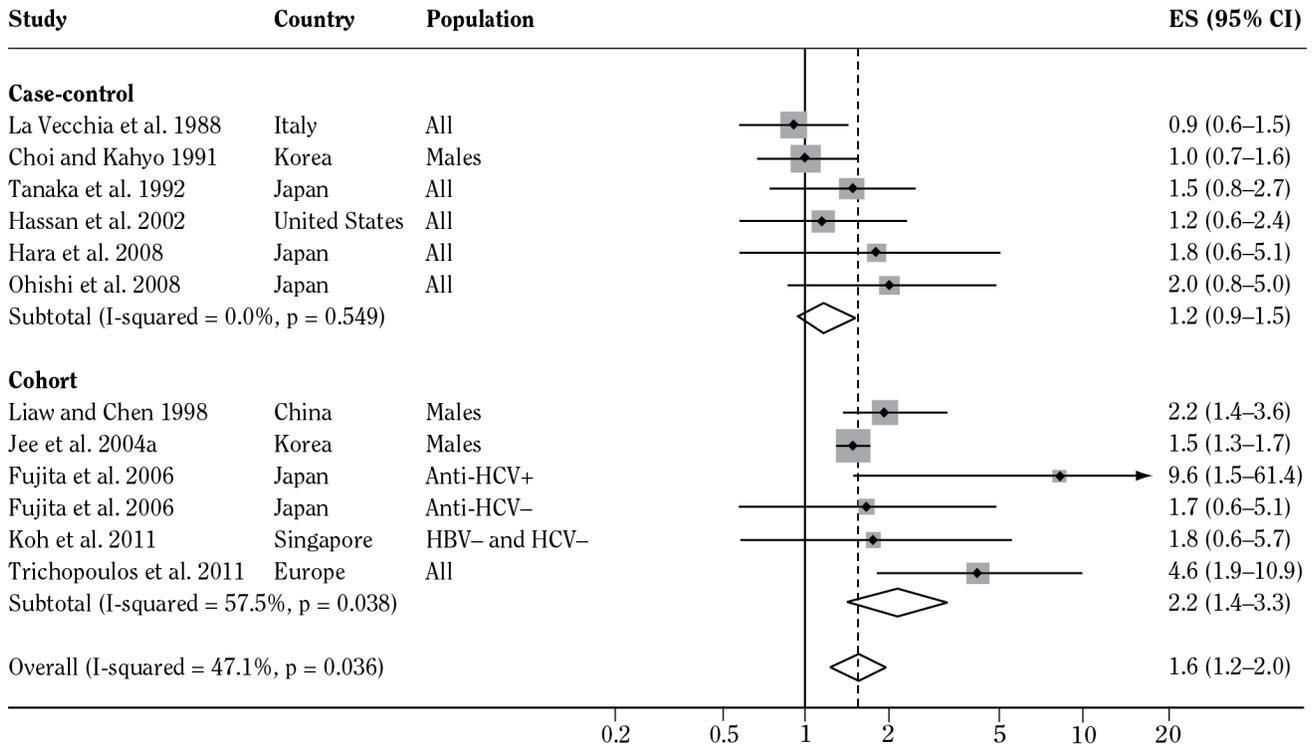
In countries in sub-Saharan Africa, the present data analysis was limited to case-control studies that evaluated ever smoking. The number of cases of HCC in these studies ranged from 46–240, and all of them adjusted for HBV or HCV infection and consumption of alcohol. Each study suggested an association between smoking and HCC, but

Figure 6.17 Estimated risk for liver cancer in current smokers compared with nonsmokers



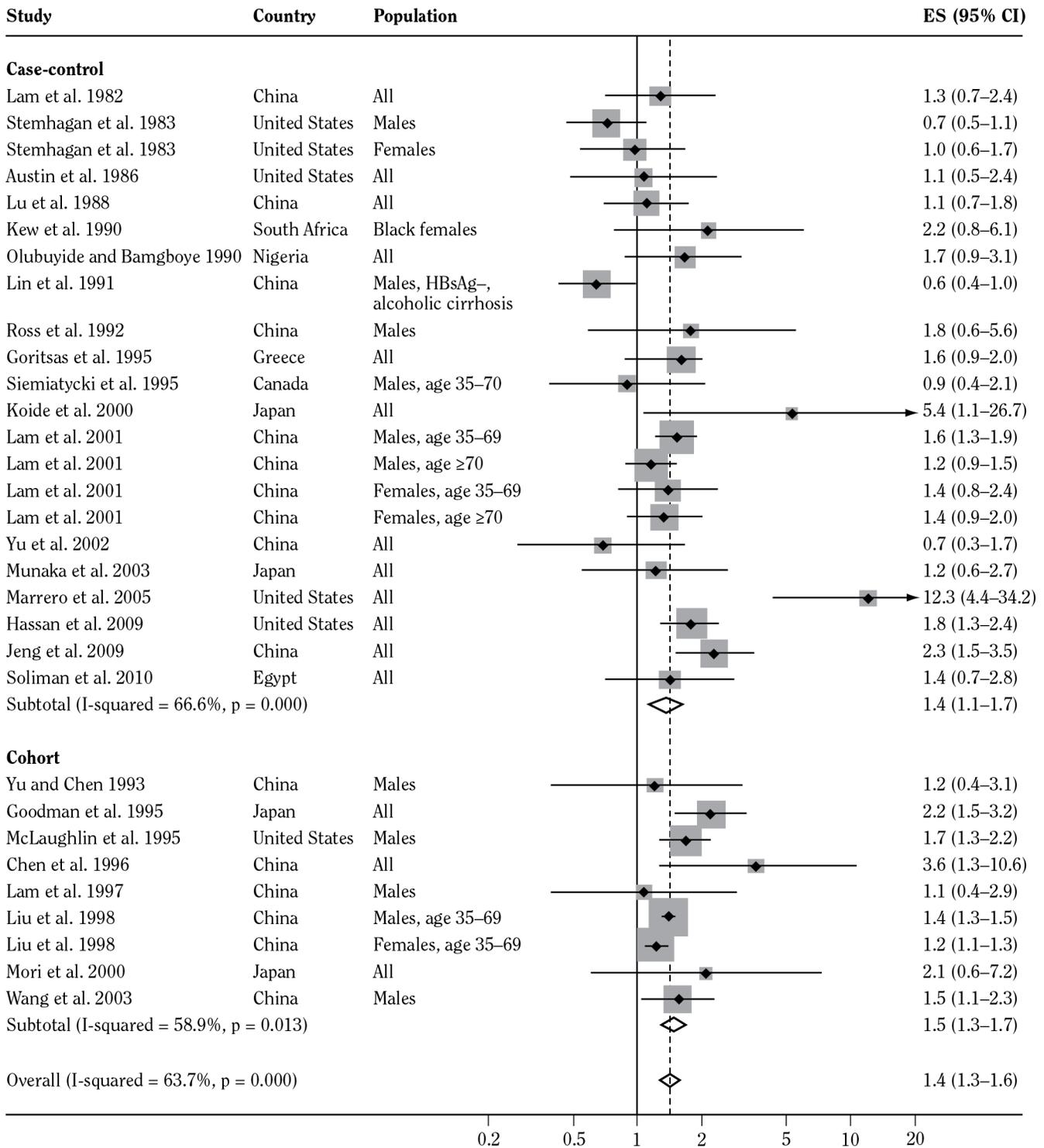
Note: Weights are from random effects analysis. CI = confidence interval; ES = effect size; HBV = hepatitis B virus; HCV = hepatitis C virus.

Figure 6.18 Estimated risk for hepatocellular carcinoma in current smokers compared with nonsmokers among studies that controlled for confounding by primary etiological factors (viral hepatitis, consumption of alcohol)



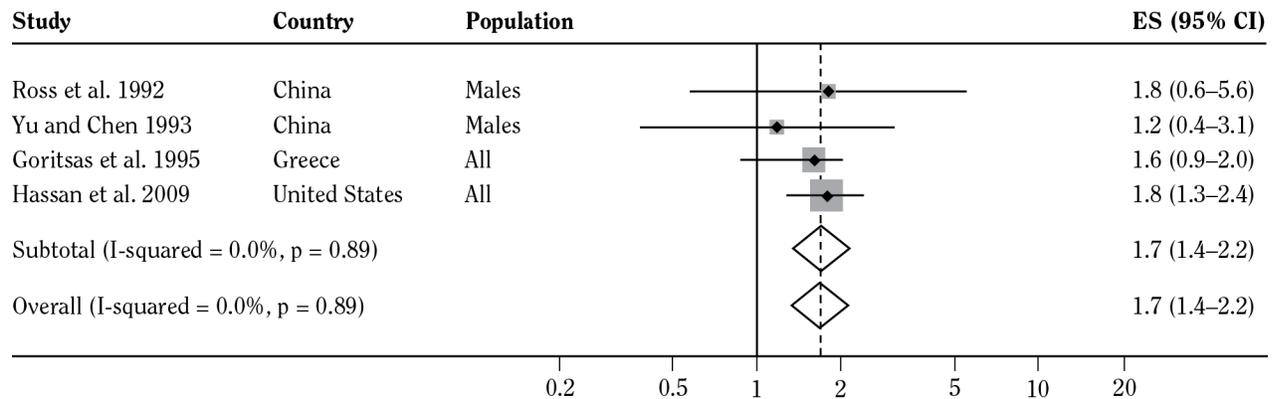
Note: Weights are from random effects analysis. CI = confidence interval; ES = effect size; HBV = hepatitis B virus; HCV = hepatitis C virus.

Figure 6.19 Estimated risk for hepatocellular carcinoma in ever smokers compared with never smokers



Note: Weights are from random effects analysis. CI = confidence interval; ES = effect size; HBsAg = hepatitis B surface antigen.

Figure 6.20 Estimated risk for hepatocellular carcinoma in ever smokers compared with never smokers among studies that controlled for confounding by primary etiological factors (viral hepatitis, consumption of alcohol)



Note: Weights are from random effects analysis. CI = confidence interval; ES = effect size.

none of them were statistically significant—likely because of the limited number of cases. Overall, the RR from the three studies with data available (Kew et al. 1990; Olubuyide and Bamgboye 1990; Soliman et al. 2010) for countries in Africa was 1.7 (95% CI, 1.1–2.5).

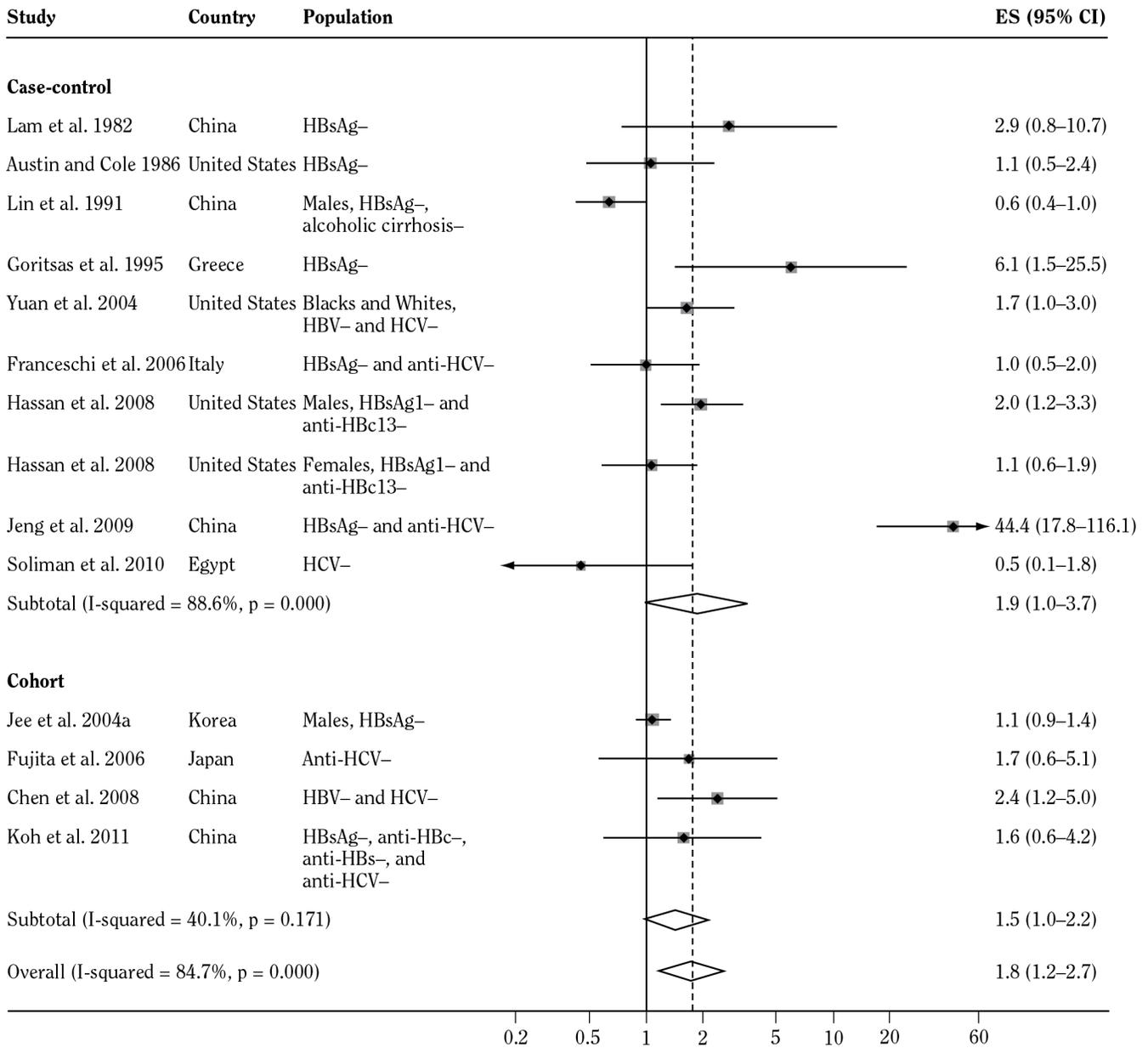
Eight studies evaluated current or ever smoking and risk for HCC in the United States (Stemhagen et al. 1983; Austin and Cole 1986; Hsing et al. 1990; McLaughlin et al. 1995; Hassan et al. 2002, 2009; Marrero et al. 2005; Zhu et al. 2007). Veterans of the armed services were substantially overrepresented in these studies. The overall RR estimate in an analysis that combined current and ever smoking was 1.8 (95% CI, 1.3–2.5), and substantial heterogeneity in estimated risk was not found by study design.

Among the 14 studies reviewed from countries in Europe, 11 were case-control studies, largely from southern Europe, and 3 were cohort studies. Substantial heterogeneity was observed in these studies. In a series of case-control studies from Greece, smoking was consistently associated with HCC, but the associations were more pronounced (and statistically significant) among HBV-negative persons (Trichopoulos et al. 1980, 1987b; Tzonou et al. 1991; Goritsas et al. 1995). After adjusting for HBV and HCV infection, a study from Greece by Kuper and colleagues (2000) demonstrated a 1.5- and 1.6-fold nonsignificant increase in risk of HCC among persons smoking fewer than or at least 40 cigarettes per day, respectively. Elsewhere, 4 case-control studies from Italy reported null findings (Filippazzo et al. 1985; La Vecchia

et al. 1988; Gelatti et al. 2005; Franceschi et al. 2006). In 2 cohort studies from Sweden, the risk estimate in 1 study among females was less than 1.0 (RR = 0.7; 95% CI, 0.2–2.0) (Nordlund et al. 1997). But, the other study observed increased rates of mortality from liver cancer among a cohort of men and a significant dose-response association with increased smoking (Carstensen et al. 1987). In a Europe-wide cohort study, Trichopoulos and colleagues (2011) rigorously characterized the smoking behavior, alcohol consumption, diet, and viral hepatitis status of a half-million people. Overall, the RR for HCC among current smokers compared to never smokers was 4.6 (95% CI, 1.9–10.9), and the RR was notably higher among males (5.4; 95% CI, 1.7–16.8) than among females (1.7; 95% CI, 0.3–8.5). In addition, the authors estimated that smoking contributed to nearly one-half of the number of cases of HCC, exceeding the proportion of HCC attributable to HBV, HCV, or consumption of alcohol. Finally, in a quantitative analysis for the present review from 5 evaluable studies in Europe, the RR for HCC among current or ever smokers (La Vecchia et al. 1988; Goritsas et al. 1995; Nordlund et al. 1997; Farker et al. 2003; Franceschi et al. 2006) was 1.4 (95% CI, 1.0–2.3).

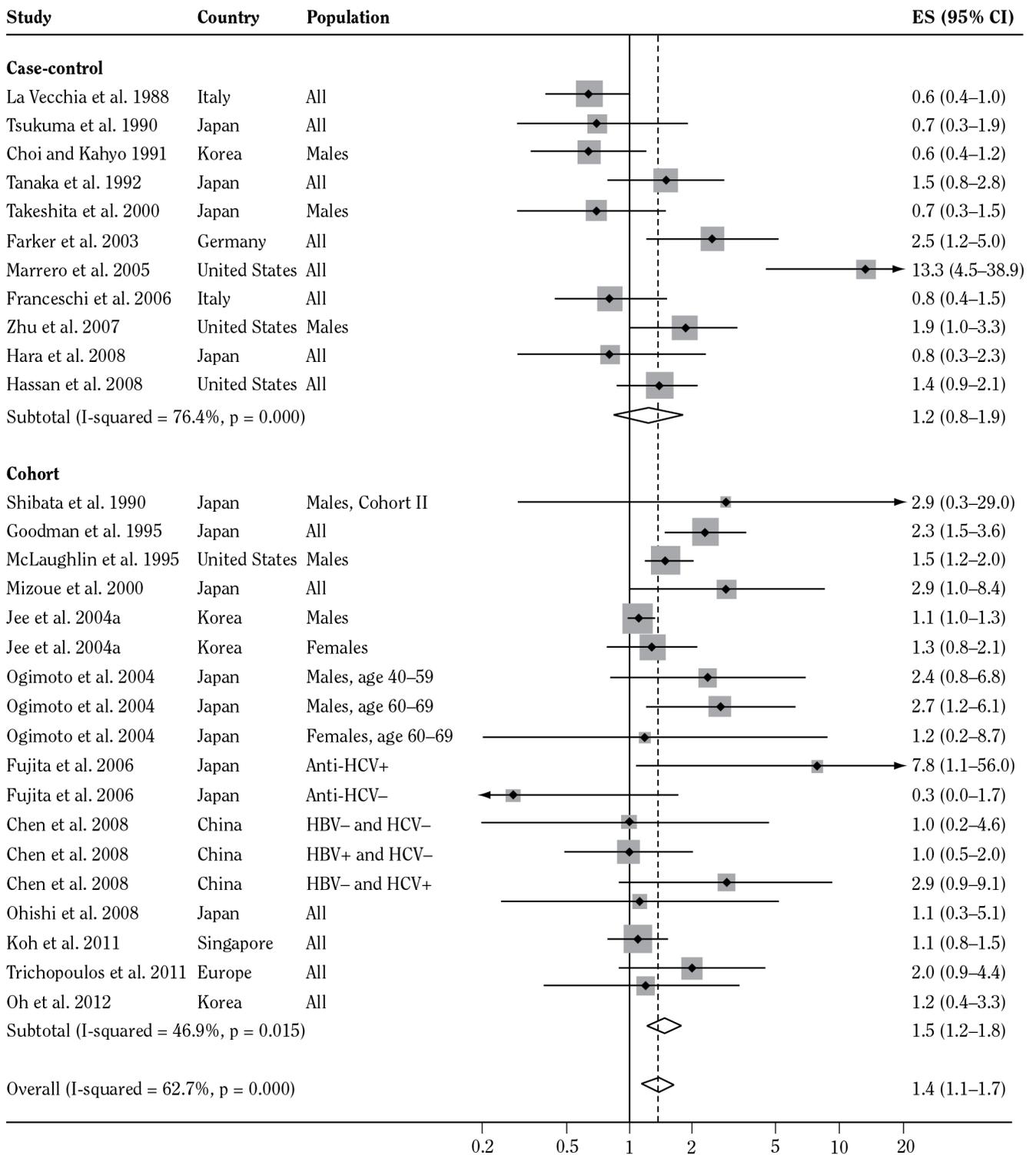
Similar to the experience in Greece, several studies from other regions suggested a higher risk of liver cancer with smoking among HBV-negative persons than among those who were HBV positive (Lam et al. 1982; Yu et al. 1991a; Chen et al. 2008). Some other studies, however, failed to find any difference in this risk by HBV status (Kew

Figure 6.21 Estimated risk for hepatocellular carcinoma among persons without evidence for chronic viral hepatitis infection for current or ever smokers compared with never smokers



Notes: Weights are from random effects analysis. **CI** = confidence interval; **ES** = effect size; **HBc13** = hepatitis B virus core 13; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus.

Figure 6.22 Estimated risk for hepatocellular carcinoma in former smokers compared with never smokers



Notes: Weights are from random effects analysis. CI = confidence interval; ES = effect size; HBV = hepatitis B virus; HCV = hepatitis C virus.

et al. 1985; Mohamed et al. 1992; Evans et al. 2002). And yet, according to eight studies published in 2000 or later, smokers with chronic HBV or HCV infection have a substantially higher risk for HCC than those who do not have chronic hepatitis infection (Mori et al. 2000; Wang et al. 2003; Jee et al. 2004a; Franceschi et al. 2006; Fujita et al. 2006; Hassan et al. 2008; Jeng et al. 2009; Soliman et al. 2010). Formal evaluations of interactions between smoking and HBV or HCV infections have been reported infrequently from these studies.

Although the present review focuses on HCC, which represents a substantial majority of primary liver cancer, a meta-analysis by Wenbin and colleagues (2013) reported on the association between smoking with gallbladder cancer. In an analysis of data from 1,158 cases across 11 studies (all but 1 were case-control), smokers had a significantly increased risk for gallbladder cancer (RR = 1.5; 95% CI, 1.1–1.9) compared with nonsmokers.

Evidence Synthesis

Overall, a substantial body of evidence documents the association between smoking and primary liver cancer. The role of the liver as a primary site for metabolism of several recognized carcinogens provides strong biologic plausibility for a causal association between smoking and HCC. In epidemiologic studies from various geographic regions and with different designs, findings demonstrate a consistent but nonuniform association between smoking and primary liver cancer. In 2004, IARC classified smoking as a cause of HCC. In the meta-analysis by Lee and colleagues (2009), which updated the evidence considered in the 2004 IARC report, the overall OR showed a moderate association, with an estimated 50% increased risk of liver cancer associated with current smoking.

In the expanded meta-analysis included in this report, 113 studies were identified that reported data on the risk of liver cancer from smoking. In the primary analysis, which focused on studies of HCC that compared current and never smokers, the overall estimate from 31 studies with evaluable data indicated that current smoking increases risk for HCC by approximately 70% (Figure 6.17). Although confounding by consumption of alcohol and HBV or HCV infection status may bias the findings of some studies, controlling for these risk factors does not fully account for the effects seen. In 11 higher quality studies that adjusted adequately for potential confounding factors, risk of HCC from smoking was moderated only slightly (60% increased risk) (Figure 6.18). Importantly, when analyses of data were restricted to persons without

chronic HBV or HCV infection, the risk for HCC from smoking remained significantly increased.

Data combined from 26 studies indicated a 40% increased risk of HCC from ever smoking (Figure 6.19). Furthermore, the effect of ever smoking on risk of liver cancer was strengthened in the studies that addressed primary confounding factors. Risk for liver cancer was significantly increased in former smokers compared with never smokers, although risk for former smokers was attenuated relative to risk for current smokers. While heterogeneity was observed in studies that evaluated dose-response associations, meta-analysis of a limited number of studies with data that could be combined suggested that increased smoking intensity increases the risk for liver cancer.

The finding of increased risk for liver cancer from smoking was generally consistent regardless of geography or study design. The greatest number of studies originated from Asia, and quantitative analysis from this region indicated a 50% increased risk of liver cancer from smoking. The estimated risk for liver cancer associated with smoking increased to 70–80% in studies from Africa and the United States. Greater heterogeneity was observed in studies from Europe than elsewhere. Several hospital-based case-control studies from southern Europe reported null or nonsignificant associations and the overall relationship between smoking and liver cancer was thus notably smaller in Europe.

Modification of the effect of smoking on risk for liver cancer by viral hepatitis has been suggested, although formal statistical evaluation remains limited. Stronger associations between smoking and HCC among persons who are negative for HBV infection have been observed in studies conducted on selected populations in Europe and China. In contrast, most studies from diverse regions—such as Asia, Egypt, Europe, and the United States—have found greater risks for liver cancer from smoking among persons with chronic HBV or HCV infections.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and hepatocellular carcinoma.

Implications

The burden of liver cancer is increasing in many regions of the world, notably due to HCV-related cases of HCC occurring in more developed countries. Among such persons, smoking also increases risk and consequently

incidence and death rates related to liver cancer may continue to grow substantially in the more developed countries with rising HCC. In high-burden regions of the world where vaccination against HBV or reductions in exposure to aflatoxin are being achieved, rates of liver cancer are

expected to decline. However, if smoking increases in these low- and middle-income countries, then the potential for reducing liver cancer from these preventive interventions will not be fully realized.

Colorectal Cancer

Colorectal cancer—that is, cancer of the colon or rectum—is the third most common type of cancer in the United States and also ranks third as a cause of cancer deaths among men and women in the United States (Siegel et al. 2013). For 2013, the ACS projected 102,480 new cases of cancer of the colon and 40,340 new cases of cancer of the rectum as well as 51,710 deaths from the two cancers combined (Siegel et al. 2013). In the mid-1990s, the lifetime probability of developing colorectal cancer was estimated to be 5.6% in the United States (Howlader et al. 2013).

Worldwide, incidence and death rates for colorectal cancer vary more than 10-fold among countries. The highest rates occur in Australia/New Zealand, Japan, North America, and Western Europe, and the lowest rates are seen in countries with developing economies, particularly in Africa and Asia (Parkin et al. 1999). Studies show that among immigrants moving from low- to high-incidence countries, rates increase within one generation to the approximate rates of the new country, suggesting a strong role for environmental agents (Thomas and Karagas 1987). Risk also varies substantially even within countries. For example, in a study by Wei and colleagues (2009) of a middle-aged cohort of U.S. women, risk to age 70 varied up to 10-fold based on lifestyle factors.

An increased risk of colorectal cancer has been linked to a variety of risk factors, including physical inactivity (Wolin et al. 2009); obesity (Renehan et al. 2008); low calcium levels (Cho et al. 2004); and alcohol intake (Thun et al. 1997). Risk for colorectal cancer also increases for persons with a family history of colorectal cancer or polyps (Fuchs et al. 1994). Finally, a high-meat diet and a diet low in vegetables, fruits, or folate (World Cancer Research Fund/American Institute for Cancer Research 2007) have been implicated.

Conversely, several factors are consistently associated with a reduced risk of colorectal cancer, including the use of aspirin and other nonsteroidal anti-inflamma-

tory drugs (NSAIDs). Aspirin use of 10–20 years is associated with a decreased risk of colorectal cancer mortality (Flossmann and Rothwell 2007), and short-term or current use of hormone replacement therapy (HRT) reduces risk in women (Rossouw et al. 2002). In addition, higher levels of vitamin D may protect against adenomatous polyps and incidence, recurrence, and death from colorectal cancer (Ng et al. 2009; Giovannucci 2010). Calcium supplementation reduces the risk of recurrent polyps (Baron et al. 1999).

The hypothesis that prolonged cigarette smoking may increase the risk of colorectal cancer gained support in the mid-1990s when epidemiologic studies, particularly cohort studies, showed a high incidence of adenomatous polyps and/or colorectal cancer in long-term smokers (Giovannucci et al. 1994a,b). Initially, there was concern that this observed association reflected uncontrolled confounding factors, such as lifestyle characteristics, as well as differences in risk between colon and rectal cancer, which are often combined in epidemiologic studies. Subsequent studies suggested a stronger relationship between smoking and rectal cancer than between smoking and colon cancer (Terry et al. 2002b; Wei et al. 2004). This difference was confirmed in two meta-analyses that were limited to prospective cohort studies (Liang et al. 2009; Tsoi et al. 2009) and one that included both case-control and cohort study data (Botteri et al. 2008a). In the latter systematic review, Botteri and colleagues searched the literature through May 2008 and evaluated data from six studies that compared the association of smoking and colon cancer separately from smoking and rectal cancer mortality. The RRs of ever smokers and current smokers were significantly higher for rectal cancer mortality than for colon cancer (rectal cancer: ever vs. never smoker, RR = 1.4 [1.2–1.7], current vs. never smoker, RR = 1.6 [1.3–1.8], colon cancer: ever vs. never smoker, RR = 1.2 [1.0–1.4], current vs. never smoker, RR = 1.2 [1.1–1.3]) (Botteri et al. 2008a).

Conclusions from Previous Surgeon General's Reports

Until the 2001 Surgeon General's report on women and smoking (USDHHS 2001), the reports of the Surgeon General on smoking had not considered the relationship of smoking with cancers of the colon and rectum. The 2001 Surgeon General's report concluded that "Women who smoke may have increased risk for ... colorectal cancer" (p. 231). IARC reported in 2004 that "There is some evidence from prospective cohort studies and case-control studies that the risk of colorectal cancer is increased among tobacco smokers," but noted that "Inadequate adjustment for various potential confounders could account for some of the small increase in risk that appears to be associated with smoking" (p. 1183). The 2004 Surgeon General's report, after reviewing extensive evidence, concluded that the evidence is suggestive but not sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Biologic Basis

Most cancers of the colon and rectum are adenocarcinomas. These tumors typically develop from clonal expansions of mutated cells through a series of histopathologic stages—from single crypt lesions to benign tumors (adenomatous polyps) to metastatic carcinomas—that take place over a span of 20–40 years (Fearon and Vogelstein 1990). The number and order of genetic and epigenetic changes in tumor suppressor genes (such as *APC*, *P53*, and *DCC*) and oncogenes (such as *RAS*) determine the probability of tumor progression (Fearon and Vogelstein 1990). On the basis of the observation that mutations of the *APC* gene on chromosome 5q are found as frequently in small adenomatous polyps as in cancers, the loss of normal *APC* function is considered an early (and possibly initiating) event in colorectal tumorigenesis (Powell et al. 1992; Morin et al. 1997). Products of the *APC* gene influence cell proliferation, adhesion, migration, and apoptosis. Activating mutations in codons 12 and 13 of the *RAS* oncogene are important in the progression of adenomas but are not directly involved in malignant transformations in the bowel (Bos 1989; Ohnishi et al. 1997). However, *KRAS* does have a role in advanced colorectal cancer (Fearon 2011). In addition, some studies suggest that smokers develop adenomas without *KRAS* mutations (Wark et al. 2006). Slattery and colleagues (2000) related smoking to microsatellite instability (a genetic marker) in colon tumors, and Curtin and colleagues (2009a) showed microsatellite instability in rectal tumors that were

diagnosed in current smokers. Approximately 85% of colorectal cancers show inactivating mutations of the *p53* tumor suppressor gene on chromosome 17p, resulting in loss of the ability to arrest cell growth and/or produce apoptosis; these mutations are important at a late stage in malignant transformation (Hollstein et al. 1991). Clonal expansion of colorectal tumors containing mutant *p53* genes gains a selective survival advantage for these tumors and they become increasingly invasive and metastatic.

Cigarette smoke contains many carcinogens, PAHs, heterocyclic aromatic amines, and *N*-nitrosamines (Hoffmann and Hoffmann 1997) that can reach the large bowel via the circulatory system (Giovannucci and Martinez 1996). One study documented that DNA adducts to metabolites of B[a]P, a potent PAH, in colonic mucosa occur more frequently and at higher concentrations in smokers than in nonsmokers (Alexandrov et al. 1996); this study provides direct evidence that tobacco carcinogens bind to DNA in the human colonic epithelium. Moreover, DNA adduction levels in the colonic epithelium were found in one study to be higher in tumor tissue from persons with colorectal cancer than from control subjects (Pfohl-Leskowicz et al. 1995).

Other genes known to be important in colorectal cancer include mismatch repair genes associated with the hereditary familial syndrome, nonpolyposis colorectal cancer, or sporadic cases of colorectal cancer (Liu et al. 1995; Thibodeau et al. 1998). One study associated cigarette smoking with a mismatch repair deficiency in colorectal cancer, as reflected by a sixfold increase in the risk of microsatellite instability in tumors in current smokers compared with nonsmokers (Yang et al. 2000). Elsewhere, in a large case-control study of incident colon cancer, Curtin and colleagues (2009b) evaluated base excision repair and observed a twofold increase in the risk of tumor mutations in current and former smokers. More generally, research continues to provide insight into pathways by which smoking could increase risk for colorectal cancer (Campbell et al. 2009).

To date, the association between cigarette smoking and colorectal cancer has not been found to be modified by polymorphisms of genes that are important in the detoxification of carcinogens found in tobacco smoke, including *GSTM1*, *GSTT1*, and *NAT2* (Gertig et al. 1998; Slattery et al. 1998). Studies of colorectal adenomas have found no modification of the risk of cigarette smoking by polymorphisms of *GSTM1*, *NAT2*, or cytochrome P4501A1, an enzyme important in the activation of PAHs (Lin et al. 1995; Potter et al. 1999). However, when researchers examined only adenomas that were 1 centimeter (cm) or larger, current smokers with the *GSTM1 null* genotype were at a higher risk than those without the *null* genotype (Lin et al. 1995). Furthermore, some evidence

suggests an increased risk of colorectal cancer and advanced polyps in smokers with *GSTI null* genotype (Ates et al. 2005). Overall, a meta-analysis of 12 studies that evaluated polymorphisms in *GSTM1* did not show any significant interaction with smoking and risk (Raimondi et al. 2009). Combined data from 7 of the 12 studies indicated that smokers with *mEH3 low- or medium-metabolizer* genotypes had a slightly lower risk of colorectal adenoma than smokers with *mEH3 high-metabolizer* genotypes. None of the other common genetic polymorphisms involved in metabolizing tobacco carcinogens modified the risk of colorectal adenoma or cancer.

Animal models of the carcinogenicity of tobacco in the colon and rectum have been limited to date and have not included studies in which the route of exposure was inhalation. In inbred male Syrian hamsters, adenocarcinomas of the colon have been produced by intrarectal instillation of B[a]P (Wang et al. 1985), and in vivo mutational assay studies found that oral administration of B[a]P to the *lacZ* transgenic mouse (Muta Mouse) induced a higher frequency of mutation in the colon than in the other organs tested (Autrup et al. 1978; Hakura et al. 1998, 1999; Kosinska et al. 1999). Finally, in vitro studies have shown that both rat and human colonic epithelium in cell cultures can enzymatically activate B[a]P (Autrup et al. 1978).

Description of the Literature Review

The published studies on cigarette smoking and colorectal adenomatous polyps and cancer cited in this section were identified by updating through December 2009 the search of the MEDLINE database from 1966 through July 2000 that was used in the 2004 Surgeon General's report. The headings "tobacco," "smoking," "colorectal adenomas," "colorectal neoplasms," "colonic neoplasms," and "rectal neoplasms" were used in the newer search. In addition, this more recent search included examination of the Web of Science and Embase, also through December 2009. Since the 1960s, the association between cigarette smoking and colorectal adenomas and cancer has been evaluated in many prospective and case-control studies; the present review extends work summarized in the 2004 Surgeon General's report and focuses on published studies that excluded cigar and pipe smokers, identified lifetime nonsmokers, and distinguished current smokers from former smokers. If multiple reports resulted from

the same prospective cohort, then the results from the longest follow-up are used unless otherwise stated.

Epidemiologic Evidence

Adenomatous Polyps

Botteri and colleagues (2008b) used rigorous search and data extraction techniques to synthesize the evidence for an association between smoking and the risk of adenomatous polyps. Among articles published from 1988–2007, they evaluated 125 in detail; these studies were conducted in countries around the world. Combined data from 33 studies found that current smokers had a significantly increased risk of adenomas (RR = 2.14; 95% CI, 1.86–2.46) (Figure 6.23). Among current smokers, the pooled RR estimates were somewhat greater (RR = 2.02; 95% CI, 0.62–6.56) for larger adenomas (≥ 10 millimeters [mm]) and those classified as high risk (RR = 2.04; 95% CI, 1.56–2.66). In addition, in a comparison with never smokers in 27 studies, former smokers had a significantly increased risk of adenomas (RR = 1.47; 95% CI, 1.29–1.67) (Figure 6.24). Finally, for every additional 10 pack-years of smoking, ever smokers had a 13% increase in risk of adenomatous polyps (95% CI, 9–18%). An evaluation for publication bias by Botteri and colleagues (2008b) showed no indication of such bias for the reporting of results about current smokers, but there was evidence for reports related to former and ever smokers.

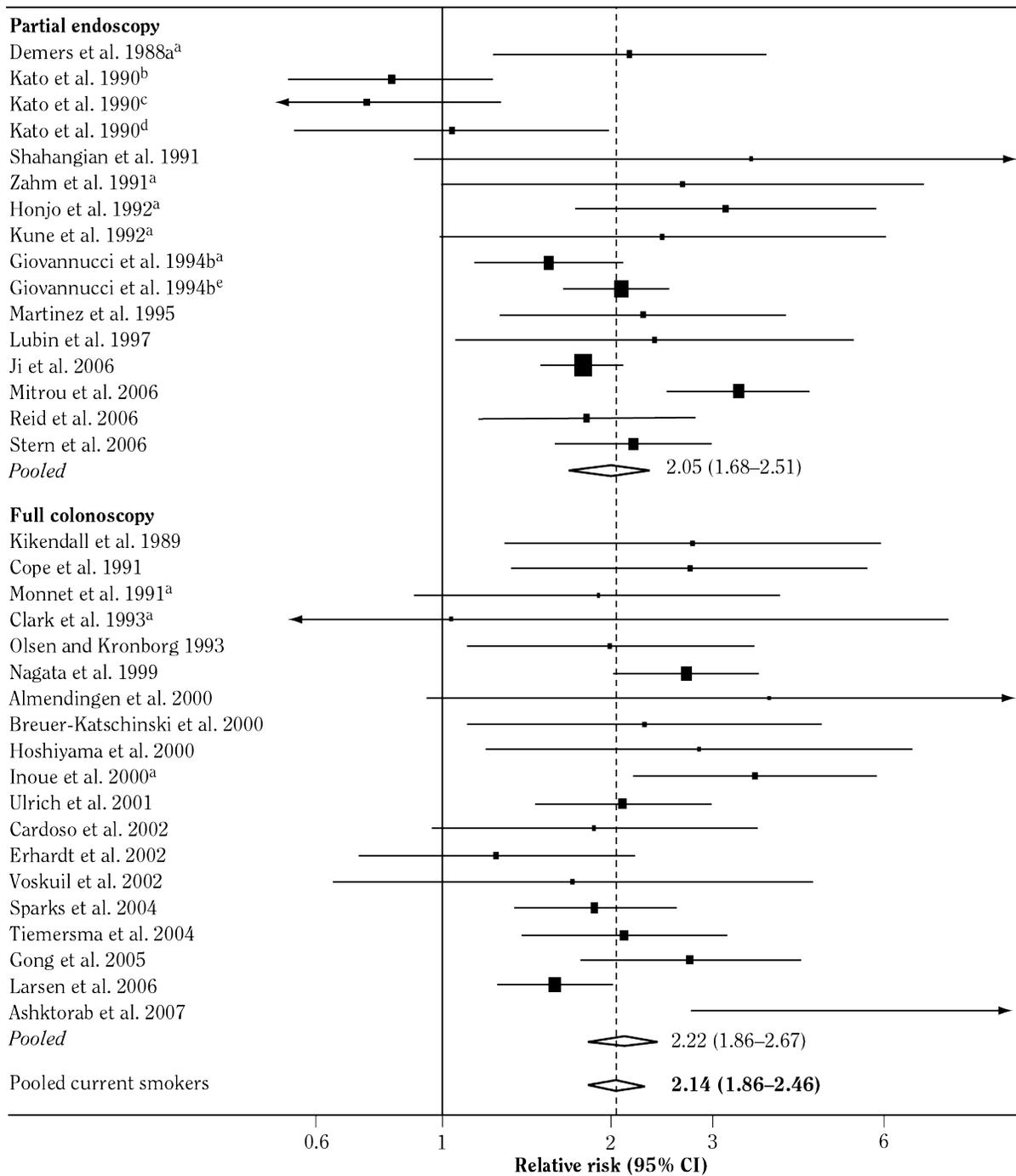
Colon and Rectal Cancer

Table 2.27 of the 2004 Surgeon General's report presented data from cohort studies of incidence and mortality for colon and rectal cancer among men and women in the United States (USDHHS 2004). Data published through 2000 and summarized in the 2004 Surgeon General's report consistently indicated that current smokers had an increased risk of colon cancer (the RRs ranged from 1.2–1.4) and of rectal cancer (RRs ranged from 1.4–2.0), regardless of the number or types of covariates for which there was adjustment.

Table 6.5S summarizes the 19 prospective cohort studies on smoking and the incidence of colorectal cancer that were published from 2002–2009. In the first study listed, Terry and colleagues (2002b) followed 89,835 Canadian women for a mean of 10.6 years and confirmed 363 cases of colon cancer and 164 of rectal cancer. The RR for rectal cancer for women with a smoking duration of 30–39 years was 1.52 (95% CI, 1.01–1.26)²; for women

²The RR does not fall within the CI. The information presented here appears just as it does on page 481 of Terry and colleagues (2002b).

Figure 6.23 Forest plot of relative risk for colorectal adenoma for current smokers versus never smokers



Source: Adapted from Botteri et al. 2008b, with permission from Elsevier, © 2008.

Note: Partial endoscopy group is composed of studies in which some or all controls underwent partial colon examination. Full colonoscopy group is composed of studies in which all controls underwent complete colon examination. CI = confidence interval.

^aEstimates for males only.

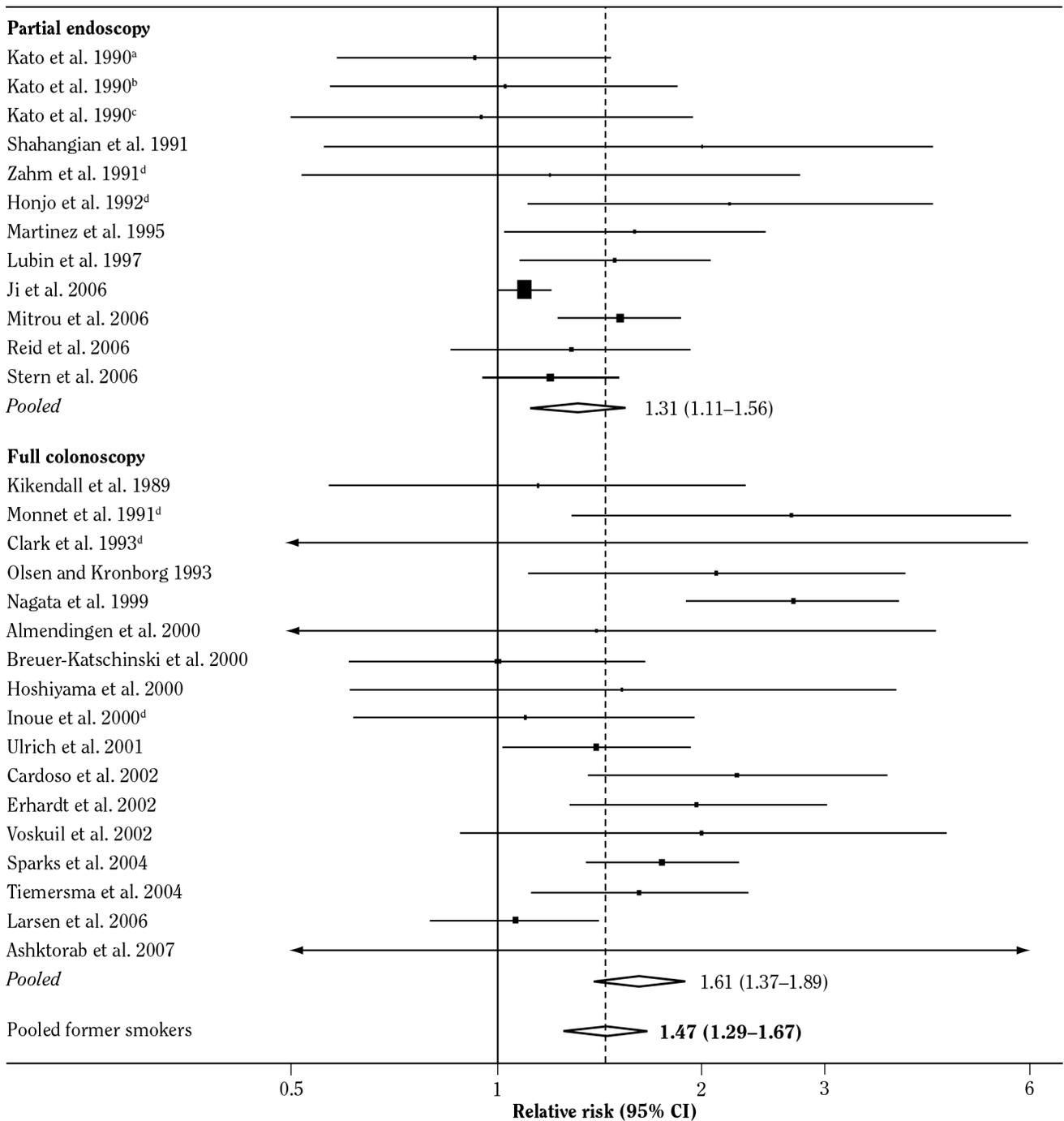
^bEstimates for distal colon.

^cEstimates for proximal colon.

^dEstimates for rectum.

^eEstimates for women only.

Figure 6.24 Forest plot of relative risk for adenomatous polyps for former smokers versus never smokers



Source: Adapted from Botteri et al. 2008b, with permission from Elsevier, © 2008.

Note: Partial endoscopy group is composed of studies in which some or all controls underwent partial colon examination. Full colonoscopy group is composed of studies in which all controls underwent complete colon examination. CI = confidence interval.

^aEstimates for distal colon.

^bEstimates for proximal colon.

^cEstimates for rectum.

^dEstimates for males only.

with duration of 40 or more years, the RR was 2.27 (95% CI, 1.06–4.87).

Tiemersma and colleagues (2002) followed 36,000 Dutch men and women who were 20–59 years of age at enrollment. At the end of follow-up (8.5 years), the investigators confirmed 102 cases of colorectal cancer. The relationship between smoking and risk for colorectal cancer was null among current smokers but significant among two groups of former smokers (durations of 16–30 and >30 years). In a U.S.-based study, Limburg and colleagues (2003) followed 34,467 women who were 55–69 years of age at baseline. The study confirmed 869 cases of colorectal cancer; duration of smoking was significantly related to risk of colorectal cancer incidence.

Per Table 6.5S, Otani and colleagues (2003) followed 90,004 Japanese men and women who were 40–69 years of age at enrollment. When the analysis was limited to invasive cases, there was a significant increase in risk among current smokers (RR = 1.6; 95% CI, 1.1–2.1) that was comparable to results when the analysis included all cases of invasive and noninvasive colon and rectal cancers.

In Japan, Shimizu and colleagues (2003), who followed 29,051 men and women for 8 years, confirmed 181 cases of colon cancer and 95 of rectal cancer. Among men, no trend was revealed between the risk of colon cancer and lifetime smoking (in pack-years), but for rectal cancer, the risk was significantly greater with more than 20 pack-years (RR = 2.44; 95% CI, 1.12–5.30) than it was for nonsmokers. In The Netherlands, a study by van der Hel and colleagues (2003a), which followed a cohort of 27,222 women, identified 249 cases of colorectal cancer. Ever smoking was similarly related (but not significantly) to colon cancer (RR = 1.36; 95% CI, 0.97–1.92) and to rectal cancer (RR = 1.31; 95% CI, 0.76–2.25).

Wakai and colleagues (2003), who followed a Japanese cohort of 25,260 men and 34,619 women for an average of 7.6 years, confirmed 408 cases of colon cancer and 204 cases of rectal cancer. Among both men and women, there was no relationship between years of smoking and risk of colon cancer or rectal cancer. In the United Kingdom, the Oxford Vegetarian Study, which followed a cohort of 11,140 vegetarians (Sanjoquin et al. 2004), confirmed 95 cases of colorectal cancer and found that risk was elevated among both former and current smokers. In Europe, The Netherlands Cohort Study on Diet and Cancer followed 58,279 men and 62,573 women (Lüchtenborg et al. 2005); during the last 5.0 years of the 7.3-year follow-up, the study identified 661 cases of colorectal cancer. The risk of colorectal cancer was elevated among former smokers (RR = 1.30; 95% CI, 1.03–1.65) but not current smokers. In Asia, Yun and colleagues (2005) followed the Korean National Health Insurance Corporation cohort of 733,134 men and identified 417 cases of colon cancer and

453 cases of rectal cancer. The risk of colon cancer was elevated among former smokers but not current smokers, while there were no significant findings for rectal cancer. In the United States, Berndt and colleagues (2006) followed 22,887 participants in the Campaign Against Cancer and Heart Disease (CLUE II) cohort from Washington County, Maryland, and confirmed 250 cases of colorectal cancer. Compared with never smokers, ever smokers in the CLUE II cohort had an increased risk of colorectal cancer that failed to reach statistical significance (RR = 1.23; 95% CI, 0.91–1.66). This analysis adjusted for age and gender but not for other risk factors for colorectal cancer.

In Korea, Kim and colleagues (2006), who followed a cohort of 14,103 men and women, confirmed 100 cases of colorectal cancer. These investigators found that duration of smoking was significantly related to risk of colorectal cancer: for those who had smoked more than 45 years, the RR was 2.35 (95% CI, 1.16–4.74) in a comparison with never smokers. Also in Asia, Akhter and colleagues (2007) followed a cohort of 25,279 Japanese men (40–64 years of age at baseline) for a mean of 7 years and identified 188 cases of colorectal cancer. These researchers observed a significant increase in risk among former smokers and a statistically insignificant, modestly increased risk among current smokers. Both age at initiation and duration of smoking were related to risk. In the United States, Paskett and colleagues (2007) analyzed data from 146,877 participants in the Women's Health Initiative (WHI). After nearly 8 years of follow-up, the study confirmed 1,075 cases of colon cancer and 176 cases of rectal cancer. The study did not find a significant relationship between smoking and risk of colon cancer, but current smokers had a significantly elevated risk of rectal cancer (RR = 1.95; 95% CI, 1.10–3.47). Duration of smoking was associated with risk of colon cancer (p-trend = 0.03) and rectal cancer (p-trend = 0.05).

Among a cohort of Chinese men and women in Singapore, Tsong and colleagues (2007) confirmed 516 cases of colon cancer and 329 cases of rectal cancer during a mean follow-up of 11 years. In this cohort, both current and former smoking were related to risk of rectal cancer but not to risk of colon cancer. Similarly, age at initiation and duration of smoking were related to risk of rectal cancer but not to risk of colon cancer. In the United States, a study by Driver and colleagues (2007) reported on follow-up results for male physicians in the Physicians' Health Study; after 20 years of follow-up, there were 381 confirmed cases of colon cancer and 104 confirmed cases of rectal cancer. Overall, ever smoking was related to risk of colorectal cancer (RR = 1.42; 95% CI, 1.17–1.72). In addition, current smokers who smoked two packs per day had an increased risk of colon cancer (RR = 1.53; 95% CI, 1.02–2.29) and rectal cancer (RR = 1.92; 95% CI, 1.01–

3.66). In Maryland, Hooker and colleagues (2008) evaluated incidence of rectal cancer in two cohorts of residents from that state's Washington County. In the cohort that was followed from 1963 to 1978, there was a significant increase in risk of rectal cancer among current male smokers but not among their female counterparts. The RR for rectal cancer in the cohort followed from 1975 to 1994 ranged from 1.57 to 1.92 for current and former smokers, but only the RR for former female smokers (1.87; 95% CI, 1.02–3.45) reached significance.

Also in the United States, Hannan and colleagues (2009) studied 184,187 men and women as part of the Nutrition cohort of the CPS-II. After 13 years of follow-up, the study confirmed 1,962 cases of colorectal cancer. Current smokers had an increased risk of colorectal cancer (RR = 1.27; 95% CI, 1.06–1.52), as did former smokers (RR = 1.23; 95% CI, 1.11–1.36). Among current smokers, the RR was greatest for those with a long duration of smoking. RR was comparable between men and women. Finally, a study by Gram and colleagues (2009) followed 68,160 women in Norway and confirmed 425 cases of colorectal cancer. Duration of smoking was significantly related to overall risk of colorectal cancer, but when individual sites were evaluated, sparse data limited the power to find significant associations. Increasing pack-years smoked was related to increased risk of colorectal cancer.

Table 6.6S summarizes 16 case-control studies published from 2001–2008; here the findings are mixed, with only a few studies reporting significant increases in risk associated with various measures of smoking. The studies were carried out in diverse locations, including Asia, North America, and Europe. Sample sizes ranged up to 2,000 cases and adjustments were made for a variety of risk factors.

Table 6.7S presents details on nine cohort studies that reported mortality data for either colorectal cancer overall or separately for colon and rectal cancer. The cohort studies of mortality also came from North America, Asia, and Europe. In several studies, risk for death from colorectal cancer was significantly increased; for example, in two studies among women in the United States—the Nurses' Health Study (NHS) (Kenfield et al. 2008) and the Iowa Women's Health Study (Limburg et al. 2003)—current smokers have an approximate 60% increased risk of colorectal cancer mortality. Several of these studies summarized in Table 6.7S also observed significant increases in risk based on number of cigarettes smoked per day or total pack-years.

Most of these studies were summarized in the three separate meta-analyses referenced earlier in this chapter (Botteri et al. 2008a; Liang et al. 2009; Tsoi et al. 2009). Notably, the meta-analysis by Botteri and colleagues (2008a) combined data from 53 studies (33 prospective

cohort and 20 case-control) that were published from 1980–2008 and further characterized the association of smoking with colorectal cancer. Drawing on 47 of those studies, the authors found that former smokers had an increased risk of colorectal cancer (RR = 1.17; 95% CI, 1.11–1.22) in comparison with never smokers. In addition, based on 25 of the studies, ever smokers had an increased risk of colorectal cancer (RR = 1.18; 95% CI, 1.11–1.25) compared with never smokers. This meta-analysis also evaluated risk for colorectal cancer mortality; based on 14 and 12 studies, respectively, current smokers (RR = 1.28; 95% CI, 1.15–1.42) and former smokers (RR = 1.23; 95% CI, 1.14–1.32) had an increased risk of mortality from colorectal cancer in a comparison with never smokers (Botteri et al. 2008a). The increased mortality could reflect a higher incidence of colorectal cancer in smokers or an unfavorable effect on the disease's natural history.

Evidence Synthesis

Taken as a whole, the results of the studies summarized in Tables 6.5S–6.7S, which come from millions of person-years of follow-up, confirm the findings of three meta-analyses for colorectal cancer (Botteri et al. 2008a; Liang et al. 2009; Tsoi et al. 2009). The individual studies have addressed cancers of the colon and rectum separately, as well as the combined outcome of colorectal cancer. Mechanistic understanding at present supports the handling of the combined outcome in synthesizing the evidence.

Although adjustments for covariates differed to some extent across the studies included in the meta-analyses, longer duration of smoking was consistently associated with increased risk of colorectal cancer. In addition, there was no evidence of heterogeneity of effect when the prospective cohort studies were combined in the three separate meta-analyses (Botteri et al. 2008a; Liang et al. 2009; Tsoi et al. 2009).

These epidemiologic data must be placed in the context of our growing understanding of the biologic etiology of colorectal cancers; researchers now have excellent insights into the sequence of genetic changes taking place from normal cells to a polyp to malignancy. The evidence now points strongly to an effect of smoking in increasing the formation of polyps, the precursor of colorectal cancer, and possibly on the development of malignancy (Botteri et al. 2008a,b; Liang et al. 2009; Tsoi et al. 2009). Furthermore, for colorectal cancer, recent findings from prospective cohort studies suggest that long-term cigarette smoking is associated with increased risk of both incidence and mortality in men as well as women. In

some studies, the risk of incidence and mortality tended to increase with longer duration of smoking and younger age at smoking initiation and to decrease with a younger age at successful cessation and a greater number of years since that took place, but the effects of these factors (age at starting or quitting and duration of smoking or time since cessation) cannot be readily separated because of their inherent correlation.

The aggregate epidemiologic evidence supports the hypothesis of Giovannucci and colleagues (1994a,b) and of Giovannucci and Martínez (1996) that a latent period of several decades is necessary for cigarette smoking to increase either the incidence of colorectal cancer or mortality from that disease and that cigarette smoking likely plays a role in early carcinogenesis in both the colon and rectum. This combined hypothesis is further supported by the consistent association between smoking and adenomas, which represents the starting point for colorectal cancer, with a doubling of risk among current smokers (Botteri et al. 2008b). Studies with null findings but only limited follow-up of long-term smokers are not informative for testing the hypothesis that a lengthy duration of smoking is needed to increase the risk of colorectal cancer. Analyses of available studies show little indication of publication bias. There is also no indication of significant heterogeneity of effect among study results.

In assessing whether cigarette smoking plays a causal role in colorectal cancer, nutrition and other factors such as physical activity and screening histories for colorectal cancer must be considered because they may confound the association. Not all of the studies to date have controlled for risk factors for colorectal cancer that may also be associated with smoking, such as physical inactivity. However, indirect evidence against confounding comes from the consistent finding of a small but

statistically significant increase in risk for colon or rectal cancer associated with smoking, regardless of the set of covariates for which there was adjustment. Furthermore, among the prospective cohort studies, many controlled for physical activity, use of alcohol, and other potential risk factors.

Cumulative findings from large prospective cohort studies show an increased risk of colon and rectal cancer after smoking for two or more decades. The evidence suggests that smoking acts in the early stages of carcinogenesis, as shown by its association with adenoma, the elevated risk for most smokers, and the associated risk with duration of smoking. The temporal pattern of the effects of smoking, with continuing increase in risk, particularly for rectal cancer and for mortality among current smokers, suggests that smoking may also act in the later stages of carcinogenesis.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Implications

The aggregate evidence indicates that cigarette smoking may be a modifiable factor that can cause colorectal cancer. Accordingly, clinicians and public health personnel should include both current and former smoking as potential risk factors for this disease.

Prostate Cancer

Among American men, prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death. In 2013, 238,590 American men were expected to be diagnosed with prostate cancer and 29,720 were expected to die from this disease (Siegel et al. 2013). Since the mid-1990s, death rates for prostate cancer have been declining, but incidence rates have fluctuated (Siegel et al. 2013). The decline in death rates has been attributed to the combination of earlier detection and advances in the treatment of men who are in advanced stages of the disease (Etzioni et al. 2008); the fluctuation in inci-

dence may be due to trends in prostate-specific antigen (PSA) testing.

To date, several risk factors for prostate cancer have been identified with certainty; these risk factors cannot be modified:

- *Age*. The risk of prostate cancer increases with age.
- *Race*. Prostate cancer incidence and death rates are highest among African American men and lowest among Asian men.

- **Family history.** Men who have a father or brother diagnosed with prostate cancer are twice as likely to be diagnosed with prostate cancer as those with unaffected fathers and brothers.

Unlike the case in breast and colon cancer, research has not yet identified the inherited mutations in genes that consistently explain the strong family associations found in prostate cancer, but some studies have discovered a small number of common variants across the genome that are associated with the risk for this disease (Eeles et al. 2008, 2009; Thomas et al. 2008).

Biologic pathways influencing prostate cancer involve hormones and growth factors. Androgens and their signaling pathways are necessary for the development of prostate cancer. Support for the role of these pathways is based on results of two trials showing that drugs inhibiting 5- α -reductases, the enzymes that convert testosterone to the more androgenic dihydrotestosterone, reduce the risk of prostate cancer (Thompson et al. 2003; Andriole et al. 2010). In epidemiologic studies, however, circulating levels of androgens have not been associated with the risk of prostate cancer (Roddam et al. 2008a). Growth factors are also important: for example, results from cohort studies have consistently associated circulating levels of insulin-like growth factor-1 with increased risk for prostate cancer (Roddam et al. 2008b). Research on pathways may provide insights into etiologic factors.

In terms of modifiable risk factors, obesity is associated with an increased risk of death from prostate cancer (Calle et al. 2003), but evidence for an association between risk for incident prostate cancer and physical inactivity is not consistent (Friedenreich and Thune 2001). Drinking alcohol does not appear to be an important factor for prostate cancer incidence or mortality (Velicer et al. 2006; Gong et al. 2009; Chao et al. 2010). Some studies have found a higher risk of prostate cancer or advanced disease with a higher intake of energy (calories), processed meat, dairy foods, and calcium, as well as lower intake of tomatoes and cruciferous vegetables (Giovannucci et al. 2007; World Cancer Research Fund 2007). Regarding prevention, two studies found reduced risk of prostate cancer as a secondary endpoint. In one study, persons who had skin cancer and lived in areas with low levels of selenium in the soil received selenium supplements (Clark et al. 1998); in the other study, men who were current or former smokers received vitamin E (Alpha-Tocopherol 1994). However, in a subsequent trial designed to test the hypothesis that supplementation with these agents would reduce the risk of prostate cancer, Lippman and colleagues (2009) found that supplementation with selenium or with vitamin E did

not reduce risk in men who were not selected for exposure to selenium or smoking status.

Conclusions from Previous Surgeon General's Reports

The relationship between smoking and risk for prostate cancer was first addressed in the 2004 Surgeon General's report on the health consequences of smoking. That report drew two conclusions: (1) the evidence is suggestive of no causal relationship between smoking and risk for prostate cancer; and (2) the evidence for mortality, although not consistent across all studies, suggests a higher mortality rate from prostate cancer in smokers than in nonsmokers (USDHHS 2004, p. 26).

Biologic Basis

Zu and Giovannucci (2009) outlined several possibilities for increased mortality from prostate cancer, including mutations in genes associated with the cancer's progression caused by carcinogenic constituents of cigarette smoke and the effects of smoking on levels of sex steroid hormones, angiogenesis, and DNA methylation. Regarding carcinogenicity and methylation, for example, loss of glutathione *S*-transferase pi expression, via hypermethylation of its gene promoter region early in the natural history of prostate cancer (Nakayama et al. 2003) may render prostate cancer cells susceptible to DNA damage as well as other kinds of damage caused by electrophiles from cigarette smoke (e.g., PAHs) (Roberts et al. 2003). In terms of hormones, compared with men who do not smoke, men who currently smoke have higher circulating levels of androstenedione—a weak androgen that is a precursor to testosterone and estradiol—and higher levels of total and free testosterone (Dai et al. 1988; Field et al. 1994; Muller et al. 2003; Shiels et al. 2009). On the other hand, former and never smokers have similar levels of total and free testosterone (Shiels et al. 2009). Because androgens are necessary for the development of prostate cancer, this pattern is consistent with the observation in some epidemiologic studies that current but not former smoking is associated with risk of death from prostate cancer. As for estradiols, some studies have found that men who smoke have higher total and free levels of this hormone than men who do not smoke (Barrett-Connor and Khaw 1987; Shiels et al. 2009). The role of estrogens in human prostate carcinogenesis is not clear.

Description of the Literature Review

To further examine the association between cigarette smoking and the risk for prostate cancer incidence, case fatality (prostate-cancer-specific mortality), and mortality from all other causes, epidemiologic studies were identified through reviews of the reference lists in the 2004 Surgeon General's report on the health consequences of smoking; published meta-analyses, expert reviews, and research articles; and through searches of the National Library of Medicine's PubMed service for research articles published after the 2004 report. The PubMed search terms used were "smoking," "cigarettes," "tobacco," "prostate cancer," "prostate neoplasms," "prostatic neoplasia," and "prostate tumor." The last PubMed search was performed April 15, 2010, for studies dating back to 2000. Case-control studies were not considered because they do not directly address factors determining incidence or provide data about mortality.

Epidemiologic Evidence

Incidence and Mortality

More than 30 prospective studies have investigated the link between smoking and incidence of prostate cancer or death from that disease; Table 6.8S summarizes the findings from studies that reported rates, risks, or RRs of prostate cancer associated with cigarette smoking. Of note, Table 6.8S presents updated findings from 8 studies that have examined five cohorts over time (see notes a–f in Table 6.8S). Epidemiologic studies of the association between cigarette smoking and prostate cancer incidence and mortality have been reviewed previously (Colditz 1996; Lumey 1996; Hickey et al. 2001; Levi and La 2001; Zu and Giovannucci 2009), including an Australian consensus conference report (Colditz 1996). To date, the association between cigarette smoking and prostate cancer has not been found to be modified by polymorphisms of genes that are important in the detoxification of carcinogens found in tobacco smoke, including *GSTM1*, *GSTT1*, and *NAT2* (Gertig et al. 1998; Slattery et al. 1998). However, some studies indicate association of xenobiotic metabolism gene SNPs with colorectal cancer and smoking (Nisa et al. 2010; Koh et al. 2011; Osawa et al. 2012; Fu et al. 2013). Meta-analyses of prospective studies (Huncharek et al. 2010) and case-control studies (Lumey 1996) have also been conducted. In the pooled analysis of data from 24 cohort studies, Huncharek and colleagues (2010) reported some evidence of increased risk for incident prostate

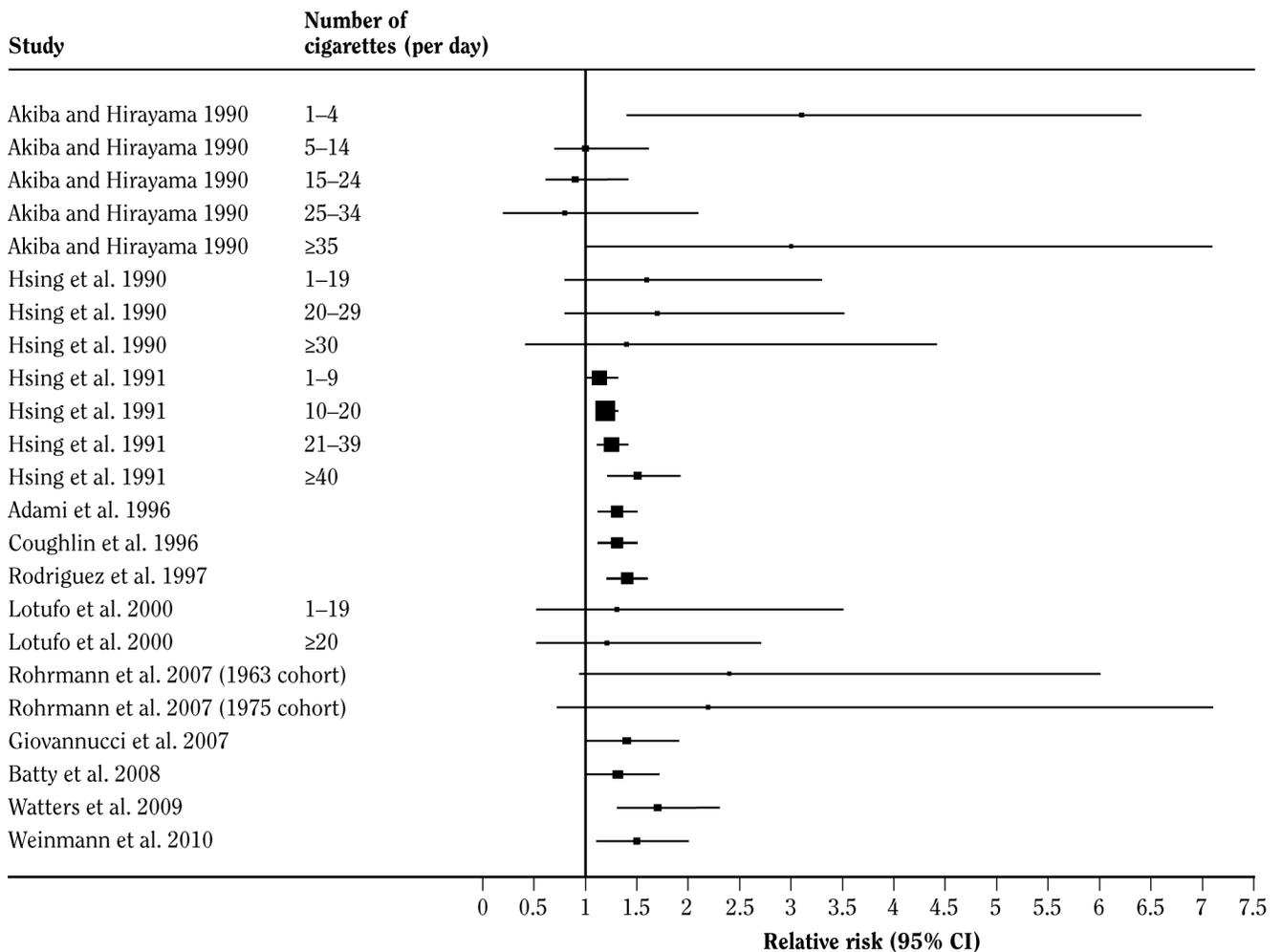
cancer (RR = 1.04; 95% CI, 0.87–1.24) among current smokers. The elevated risk was significant in data stratified by amount smoked (cigarettes per day: RR = 1.22; 95% CI, 1.01–1.46; pack-years of smoking: RR = 1.11; 95% CI, 1.01–1.22). Increased risk of deaths from prostate cancer was also found among current smokers (RR = 1.14; 95% CI, 1.06–1.19) (Huncharek et al. 2010).

Twenty-one of the 35 prospective studies reviewed in Table 6.8S did not support a positive association between cigarette smoking and risk (incidence) of prostate cancer. Four of the 35 studies supported positive associations (Whittemore et al. 1984; Hiatt et al. 1994; Adami et al. 1996; Cerhan et al. 1997), and 10 produced either null associations or findings that appeared to indicate inverse associations. Beyond the studies summarized in Table 6.8S, a nested case-control study by Heikkilä and colleagues (1999) did not reveal a baseline difference in the prevalence of current smoking between incident prostate cancer cases and controls. In another study, in a comparison with the general population, Malila and colleagues (2006) found a higher than expected incidence rate of prostate cancer in the placebo arm of the Alpha-Tocopherol, Beta-Carotene Trial of male smokers (median level of smoking at randomization: 20 cigarettes/day for 36 years): the standardized incidence ratio here was 1.20 (95% CI, 1.06–1.35) (Malila et al. 2006).

In contrast to the lack of a consistent association described above between smoking and incidence of prostate cancer, 12 prospective studies (Hammond and Horn 1958; Akiba and Hirayama 1990; Hsing et al. 1991; Tverdal et al. 1993; Adami et al. 1996; Coughlin et al. 1996; Rodriguez et al. 1997; Giovannucci et al. 2007; Rohrmann et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010) of the 20 such studies that evaluated prostate cancer mortality in Table 6.8S supported a modest-to-moderate positive association with smoking. In an investigation not included in Table 6.8S, a prospective cohort study by Eichholzer and colleagues (1999) that used non-smokers with normal levels of vitamin E as a comparison group reported a higher risk of prostate cancer death among men who smoked and had a low plasma concentration of vitamin E (RR = 3.26; 95% CI, 1.27–8.35). In contrast, no difference in risk was found among male smokers who had a normal level of vitamin E.

Unlike associations between smoking and other types of cancer such as neoplasms of the lung, the risk of prostate cancer death does not appear to rise with an increasing number of cigarettes smoked per day, duration of smoking, or total pack-years. However, current or recent smoking (Figure 6.25), rather than smoking in the distant past or a cumulative smoking history, may influence prostate cancer mortality. For example, among

Figure 6.25 Prospective cohort studies on the association between current cigarette smoking and prostate cancer mortality



Note: Includes studies reporting a relative risk and 95% confidence interval for current smoking or current number of cigarettes smoked per day. See Table 6.8S for additional studies for which confidence intervals were not reported. CI = confidence interval.

studies in Table 6.8S reporting a positive association for smoking, the RR was larger for current smokers than for former smokers (Hsing et al. 1991; Adami et al. 1996; Rodriguez et al. 1997; Giovannucci et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010) or was stronger when considering smoking status closer to the time of death from prostate cancer (Hsing et al. 1991; Rohrmann et al. 2007).

Two reports from Giovannucci and colleagues (1999, 2007) provide further evidence for the importance of relatively recent smoking. In an earlier report from the Health Professionals Follow-up Study (not shown in Table 6.8S), Giovannucci and coworkers (1999) followed participants

from 1986 to 1994 and noted 177 prostate cancer deaths in 351,261 person-years. Compared with never smokers, the RR was 1.58 for current smokers at baseline, 1.73 for men who had quit smoking within 10 years of baseline, and 1.04 for those who had quit 10 or more years before baseline. In a later report from the same study, Giovannucci and associates (1999) followed participants from 1986–2002 and noted 312 prostate cancer deaths in 673,706 person-years. Using simple updating of biennially assessed smoking status (rather than baseline smoking status, as in their 1999 report), the authors found that the RR among current smokers, in a comparison with smokers who had quit within 10 years, was 1.41 (95% CI, 1.04–1.91).

Data from some studies do not support the hypothesis that the association between prostate cancer mortality is stronger for current smoking than for former smoking (Doll et al. 2005). Their British Doctors Study, which followed physicians from 1951–2001, noted 878 prostate cancer deaths in 34,439 male physicians. The study recorded updated smoking status in 1957, 1966, 1971, 1978, and 1991. The prostate cancer mortality rate (indirectly standardized for age and study year) did not differ (Table 6.8S) between never smokers (89.4/100,000 men per year), former smokers (80.9), and current smokers (90.0). Despite the overall lack of association among smokers, however, the prostate cancer mortality rate (per 100,000 men per year) increased with the number of cigarettes smoked per day by current smokers (1–14/day = 66.7; 15–24 = 99.6; $\geq 25 = 113.3$), but the *p* for trend was not significant (0.52) (Table 6.8S).

Ten of the studies in Table 6.8S were not cited in the 2004 Surgeon General's report (Lotufo et al. 2000; Lund Nilssen et al. 2000; Putnam et al. 2000; Allen et al. 2004; Doll et al. 2005; Giovannucci et al. 2007; Rohrmann et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010). Of these, 7 reported on cigarette smoking and prostate cancer mortality (Lotufo et al. 2000; Doll et al. 2005; Giovannucci et al. 2007; Rohrmann et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010); 4 of the 7 gave quantitative support for a positive association between smoking (3 implicated current smoking) and death from prostate cancer (Rohrmann et al. 2007; Batty et al. 2008; Watters et al. 2009; Weinmann et al. 2010). Two of the 10 studies not cited in the 2004 Surgeon General's report but shown in Table 6.8S (Doll et al. 2005; Giovannucci et al. 2007) were updates of studies included in the 2004 report (Doll et al. 1994; Giovannucci et al. 1999). The findings in the 2004 report of no association with prostate cancer mortality in the British Doctors Study (Doll et al. 1994) and of a positive association in the Health Professionals Study (Giovannucci et al. 1999) were unchanged with additional follow-up.

Stage and Histologic Grade

As shown in Table 6.9S, three studies (Hussain et al. 1992; Roberts et al. 2003; Moreira et al. 2010) investigated the association between smoking and both disease stage and histologic grade at the time of diagnosis or surgical treatment, while two (Daniell 1995; Kobrinsky et al. 2003) looked at smoking and disease stage but not histologic grade. Advanced stage (e.g., local invasion, metastasis to a regional lymph node, metastasis to bone) and high grade (e.g., a high sum of the two Gleason scores given by the

pathologist or poorly differentiated cancer at pathologic examination) are indicators of a poor prognosis. Thus, studies about smoking and stage or grade of the cancer are relevant for interpreting the findings of higher mortality in the prospective studies. Cases were ascertained from a clinical setting in three studies (Hussain et al. 1992; Daniell 1995; Roberts et al. 2003), from a regional cancer registry in one (Kobrinsky et al. 2003), and from the SEARCH cohort in the fifth (Moreira et al. 2010). All five studies support the hypothesis that smokers diagnosed with prostate cancer are more likely to have advanced-stage disease or less-well-differentiated disease than men who have prostate cancer and do not smoke. In the only study that evaluated intensity of smoking, risk of extraprostatic disease or high-grade disease increased with number of pack-years of smoking (Roberts et al. 2003).

Progression, Case Fatality, and All-Cause Mortality

Nine studies have investigated the association between smoking and the progression of prostate cancer after diagnosis, death from the disease, or death from all causes in men who have prostate cancer (Table 6.10S). Eight of the studies used a retrospective cohort design, while one (Gong et al. 2008) was a prospective study. Five studies reported on progression, defined as biochemical recurrence/progression/failure, local recurrence/failure, distant failure, or development of hormone-refractory disease (Merrick et al. 2004; Oefelein and Resnick 2004; Pickles et al. 2004; Pantarotto et al. 2007; Moreira et al. 2010). Five studies reported on case fatality (Daniell 1995; Pickles et al. 2004; Jager et al. 2007; Pantarotto et al. 2007; Gong et al. 2008), and five reported on all-cause mortality (Yu et al. 1997; Oefelein and Resnick 2004; Pickles et al. 2004; Jager et al. 2007; Pantarotto et al. 2007). One study reported on death from all causes *other* than prostate cancer (Gong et al. 2008).

Of the nine studies reported in Table 6.10S, six suggest that in men who have prostate cancer, smoking is associated with a higher risk of progression or death from the disease; these findings were independent of smoking's possible influence on stage or grade. Among men diagnosed with prostate cancer, all-cause mortality appears to be higher in smokers than in nonsmokers. In some studies, many of these deaths were due to prostate cancer because the majority of men had advanced-stage disease (Oefelein and Resnick 2004). In other studies, deaths were more likely due to other causes because the majority of men had localized disease (Pickles et al. 2004; Gong et al. 2008).

Evidence Synthesis

The published literature suggests that smoking, especially current or recent smoking, is a risk factor for prostate cancer mortality but not for incidence of the disease. Findings of a positive association with prostate cancer mortality and null associations with incidence are somewhat consistent across a set of prospective cohort studies (in which temporality is clear) that have been conducted in a number of settings and across several decades. The strength of the association between current smoking and prostate cancer mortality is modest to moderate, and unlike the case with some other cancers, the strength of the association does not appear to depend on the number of cigarettes smoked per day or pack-years of smoking.

The published literature also consistently shows that in men who have prostate cancer, smoking is a risk factor for being diagnosed with disease that is already of advanced stage or of high grade, and—independent of stage and grade—is a risk factor for progression of the disease, including progression to death. Although these patterns of association are biologically plausible, the specific biologic basis is unknown at this point. Alternative explanations to a causal association cannot be completely excluded with confidence (Zu and Giovannucci 2009).

Conclusions

1. The evidence is suggestive of no causal relationship between smoking and the risk of incident prostate cancer.

Breast Cancer

Breast cancer is the most frequently diagnosed type of cancer, other than nonmelanoma skin cancers, and the second leading cause of cancer death among women (Siegel et al. 2013). Despite an approximate 2% decrease in incidence since 1999 and a 28% decline in breast cancer mortality since 1991 (Jemal et al. 2010a,b), about 211,000 new cases of invasive breast cancer were diagnosed and approximately 40,000 deaths resulted from breast cancer among U.S. women in 2009 (Howlader et al. 2013). The age adjusted incidence and death rates for 2004–2008 were 124/100,000 and 23.5/100,000 women per year, respectively, based on the 17 geographic areas covered by the SEER Program of NCI (Howlader et al.

2. The evidence is suggestive of a higher risk of death from prostate cancer in smokers than in nonsmokers.
3. In men who have prostate cancer, the evidence is suggestive of a higher risk of advanced-stage disease and less-well-differentiated cancer in smokers than in nonsmokers, and—independent of stage and histologic grade—a higher risk of disease progression.

Implications

The biologic processes underlying the suggestive association between cigarette smoking and prostate cancer mortality, case fatality, and more seriously unfavorable pathologic characteristics of the tumor require further investigation, particularly because incidence is not associated with smoking. Further research on the association between smoking and the incidence of prostate cancer is warranted because the mortality rate indicates an effect of public health significance. Additional epidemiologic studies should address the timing of cigarette smoking relative to mortality and case fatality, and laboratory-based studies should address the biologic mechanisms underlying the apparently worse phenotype of prostate cancer in smokers. The finding that the risk of prostate cancer mortality is not elevated in former smokers who quit years in the past suggests that quitting smoking may reduce prostate cancer mortality. Further research is needed to refine this temporal relationship and to quantify the benefits of cessation after a diagnosis of prostate cancer.

2013). Average annual incidence rates per 100,000 women varied substantially by race/ethnicity in 2004–2008: 77.9 for American Indians/Alaska Natives, 92.1 for Hispanics, 93.7 for Asians/Native Hawaiian or Other Pacific Islanders, 119.9 for Blacks, and 127.3 for non-Hispanic Whites. Death rates per 100,000 women also varied by race/ethnicity during this period: 12.2 for Asians/Native Hawaiian or Other Pacific Islanders, 15.1 for Hispanics, 17.2 for American Indians/Alaska Natives, 22.8 for non-Hispanic Whites, and 32.0 for Blacks.

The burden of breast cancer morbidity and mortality is high. Thus, researchers have long sought to identify modifiable etiologic factors to prevent and

control this disease. Active cigarette smoking and exposure to secondhand smoke have received increasing attention over the past two decades, as clinical studies have detected nicotine and its metabolite cotinine in the breast fluid of nonlactating women (Petrakis et al. 1978; Hill and Wynder 1979), and data from rodent studies have indicated that genotoxic carcinogens in cigarette smoke can induce mammary tumors (el-Bayoumy 1992). Sixty-nine known carcinogens are detectable among the myriad chemicals in tobacco smoke (USDHHS 2004). Adipose tissue of the breast can store lipophilic carcinogens, and these can be locally activated by breast epithelial cells to form DNA adducts (Phillips et al. 2002). The prevalence of carcinogen DNA adducts is reported to be increased in smokers and in women with breast cancer (see “DNA Adducts”). A recent report suggests that nicotine leads to overexpression of cyclin D3 and induces neoplastic transformation and proliferation of breast epithelial cells in vitro (Lee et al. 2010a). Thus, evidence is accumulating for several plausible mechanisms by which smoking may induce breast cancer; this evidence is reviewed in greater detail below.

Historically, the epidemiologic evidence for an association between breast cancer and active cigarette smoking and between breast cancer and exposure to secondhand smoke has been inconsistent, leading to conclusions in the past that smoking is not a risk factor for this type of cancer (Palmer and Rosenberg 1993; Terry and Rohan 2002). However, some recent reviews have concluded that both active and passive smoking may increase the risk of breast cancer, although there is continuing disagreement as to the magnitude of effect (California Environmental Protection Agency [Cal/EPA] 2005; Collishaw et al. 2009 for the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk; Institute of Medicine 2012).

Biologic Basis—Evidence for Potential Etiologic Mechanisms

Breast cancer is the end result of a multistep process in which some epithelial cells in the breast undergo a series of mutations. In doing so, these cells escape from programmed cell death and then proliferate and invade surrounding tissue (Armitage and Doll 1957; Fisher 1958; Cairns 1975; Tomlinson et al. 1996). Genetic and epigenetic mutations in critical genes in cells—such as tumor suppressor genes, DNA replication and repair genes, and proto-oncogenes—can lead to the initiation of tumorigenesis. Clones from these mutated cells continue to expand and proliferate, rendering them susceptible to further

cancer-causing mutations. For hereditary cancers, as proposed in the Knudson (1996) model, at least two allelic mutations are necessary, one of which might be inherited. Endogenous and exogenous exposures can potentially affect the development and proliferation of mutant cells in both inherited and sporadic breast cancer and thereby affect breast carcinogenesis.

The following section addresses biologic mechanisms by which tobacco smoke, an exogenous exposure, can potentially contribute to the causation of breast cancer. The review in this section addresses the plausibility of a causal association between risk of breast cancer and active or passive smoking. The studies were identified through literature searches using the following key words: smoking and breast cancer, carcinogenesis, DNA adducts, epigenetic, hormones (androgens, progesterones, and estrogens), anti-estrogen hypothesis, and ovarian function. Past Surgeon General's reports were also reviewed: those published in 2004 and 2006, which addressed active and passive smoking, respectively (USDHHS 2004, 2006), and the one in 2010, which focused on mechanisms by which tobacco smoke contributes to disease (USDHHS 2010).

DNA Adducts

Cigarette smoke contains thousands of compounds including 69 known to be carcinogens (USDHHS 2010). Some of these compounds have been shown to cause mammary tumors in rodents (Hecht 2002). Nicotine, one of the major constituents of tobacco smoke, has been measured in the nipple aspirate of female smokers (Petrakis et al. 1978) and smoking-related DNA adducts have been found in the DNA of epithelial cells within breast milk (Thompson et al. 2002), documenting that components of smoke reach breast tissue. Carcinogens in tobacco smoke cause cancer by damaging DNA; this is the initiating event in tumorigenesis (Figure 6.4). Many carcinogens from tobacco smoke are metabolically activated by the cytochrome P-450 (CYP) enzymes, including CYP1A1 and CYP1B1, and by NAT2, all of which are present in breast tissue. These activated metabolites bind to DNA to form DNA adducts that in turn can damage DNA (USDHHS 2010). Elevated levels of DNA adducts have been associated with certain types of cancer, supporting a positive association between increasing levels of DNA adducts and risk of cancer (Phillips 2005). The degree of activation of detoxification enzymes—such as glutathione S-transferases (GSTs), uridine-5'-disphosphate-glucuronosyltransferases (UGTs), epoxide hydrolases, and sulfatases, which are also present in the breast—is important because these enzymes catalyze the excretion of the toxic metabolites, thereby potentially decreasing the formation of DNA adducts.

Smoking induces activity of some of these enzymes (USDHHS 2010).

As a biomarker, smoking-related DNA adducts are an integrated measure of exposure to tobacco smoke, metabolic activation, and delivery of the metabolite to DNA in the target tissue (Groopman et al. 1995). Smoking-related DNA adducts can be quantified in breast fluid, tissue, and peripheral blood cells. However, an increase in the levels of DNA adducts does not directly correspond to a similar increase in cancer risk because other processes are involved (Phillips 2005). To causally link the presence of smoking-related DNA adducts to risk of breast cancer, elevated levels ideally need to be detected in breast epithelial cells before the onset of the cancer and at higher levels in those individuals going on to develop cancer than in those who do not. Levels of DNA adducts measured at the time of diagnosis or after diagnosis (e.g., in case-control or cross-sectional studies) may not reflect the etiologically relevant time window of tumor initiation. Similarly, levels of DNA adducts in peripheral cells may not reflect what is happening locally at a specific target site: circulating levels of biomarkers have not always been correlated with levels at the tissue site.

Several studies have evaluated the relationship between smoking and the prevalence of smoking-related DNA adducts in breast tissue (Perera et al. 1995; Li et al. 1996; Rundle et al. 2000). These studies have confirmed the presence of smoking-related DNA adducts in breast tumor cells and adjacent normal epithelial cells in some, but not all, current and former smokers (Perera et al. 1995; Li et al. 1996; Rundle et al. 2000; Faraglia et al. 2003). Some case-control studies have reported high levels of DNA adducts in smokers compared with nonsmokers (Perera et al. 1995; Li et al. 1999; Conway et al. 2002; Li et al. 2002; Rundle et al. 2002). Faraglia and colleagues (2003) conducted a large, comprehensive case-control study that included 148 breast tumor tissues and adjacent normal samples from the Long Island Breast Cancer Study Project. The arylamine 4-aminobiphenyl (4-ABP) DNA adduct was measured using an immunoperoxidase method that had been validated by mass spectrometry. The study's authors observed a significant trend between levels of 4-ABP DNA adducts in normal breast tissue and smoking status, and they measured higher levels of DNA adducts in active and passive smokers than in never smokers. Interestingly, mean levels of DNA adducts were significantly lower in tumor tissue than in adjacent normal tissue.

Elsewhere, circulating levels of PAH-DNA adducts in peripheral blood mononuclear cells were assessed in two sample sets taken 4.5 years apart from the same case-control study (Gammon et al. 2004b). The authors observed a modest association in both sets of samples between the

highest PAH-DNA adduct levels and the risk of breast cancer, but they did not observe a dose-response relationship with increasing adduct levels. Furthermore, the strength of the association did not differ between active and passive smokers. To date, no prospective cohort study has incorporated these markers.

Polymorphisms in genes encoding enzymes involved in the metabolic activation and detoxification of toxins, such as those from exposure to cigarette smoke, could also affect breast carcinogenesis by either promoting or preventing the formation of DNA adducts. Firozi and colleagues (2002) observed a significant interaction between levels of DNA adducts in breast tissue and *CYP1A1*, *GSTM1*, and *NAT2* polymorphisms among ever smokers. These authors also observed higher levels of DNA adducts among smokers with combined *CYP1A1**1/*2 or *2/*2 and *GSTM1 null* genotypes than among smokers with polymorphisms in either genes. In addition, the frequency of smoking-related DNA adducts was higher in those with slow acetylator alleles of the *NAT2* gene than in those having rapid acetylator alleles.

Several studies have examined the association between smoking, *p53* mutations, and/or protein expression in breast tumors; results have been mixed (Conway et al. 2002; Furberg et al. 2002; Gaudet et al. 2008; Van Emburgh et al. 2008a). Mordukhovich and colleagues (2010), who conducted a large case-control study of 859 cases and 1,556 controls from the Long Island Breast Cancer Study Project, found that women in the study with *p53*-positive tumors were less likely to have been exposed to cigarette smoke than women without *p53* mutations. This finding suggests that smoking may not significantly affect the *p53* pathway. In this study, *p53* mutations were identified from DNA extracted from paraffin blocks and *p53* protein expression was evaluated using immunohistochemistry.

Other Cellular Mechanisms

In addition to forming DNA adducts, constituents of tobacco smoke may contribute to carcinogenesis by promoting cell growth and proliferation through the activation of a number of receptors, such as cyclooxygenase II and prostaglandin E2, and signaling pathways, including Akt and epidermal growth factor receptor (Narayan et al. 2004; Miller et al. 2005; Kundu et al. 2007; Botlagunta et al. 2008; Guo et al. 2008; Connors et al. 2009; Dasgupta et al. 2009). Constituents of tobacco smoke may also cause cells to evade apoptosis after DNA damage by altering cellular response at the mRNA and protein levels (Connors et al. 2009). In addition, cigarette smoke can inactivate tumor suppressor genes via genetic and epigenetic changes (Liu et al. 2010a). Narayan and colleagues (2004)

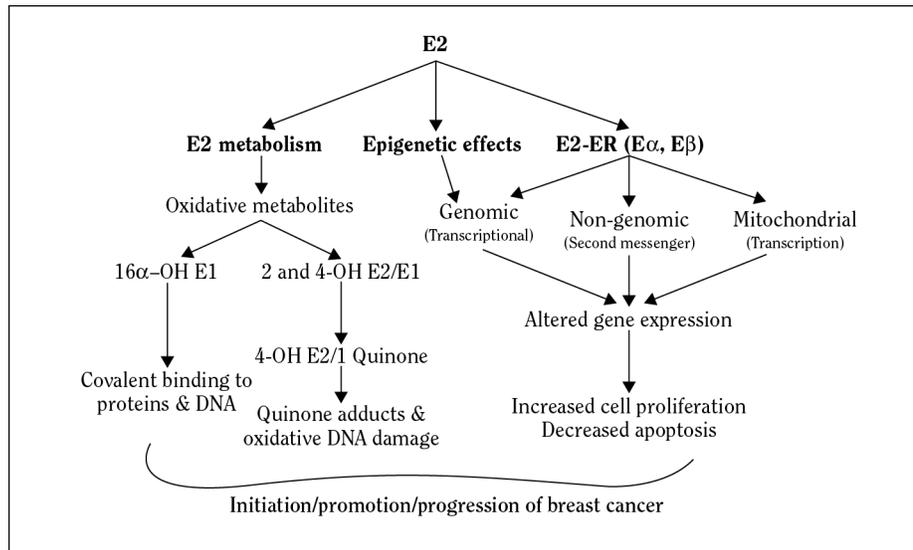
found that cigarette smoke condensate increases levels of *GADD45*—a gene whose expression is upregulated in response to DNA damage and/or growth arrest in a dose-dependent manner—to increase proliferation of epithelial cells and to induce cell cycle arrest at the synthesis/gap₂/mitosis (S/G₂/M) phase. Furthermore, Dasgupta and colleagues (2009) found that the exposure of human breast cancer cells to nicotine can contribute to epithelial-mesenchymal transition, a collection of changes seen in more advanced cancers that is characterized by loss of cell adhesion, increased cell mobility, and repression of E-cadherin. These mechanistic studies were conducted in cell culture experiments using normal and malignant breast epithelial cell lines, but they have yet to be replicated in an in vivo model.

Hormones

Estrogen's role in the initiation, promotion, and progression of breast cancer is well established through preclinical data, observational studies, and clinical trials (Yager and Davidson 2006). Studies in experimental animal models and cultured human cells demonstrate that estradiol (E2) and estrone (E1) are carcinogenic (Yager and Davidson 2006). Estrogen is thought to exert its carcinogenic effects primarily through two complementary pathways (Figure 6.26). The first pathway involves the

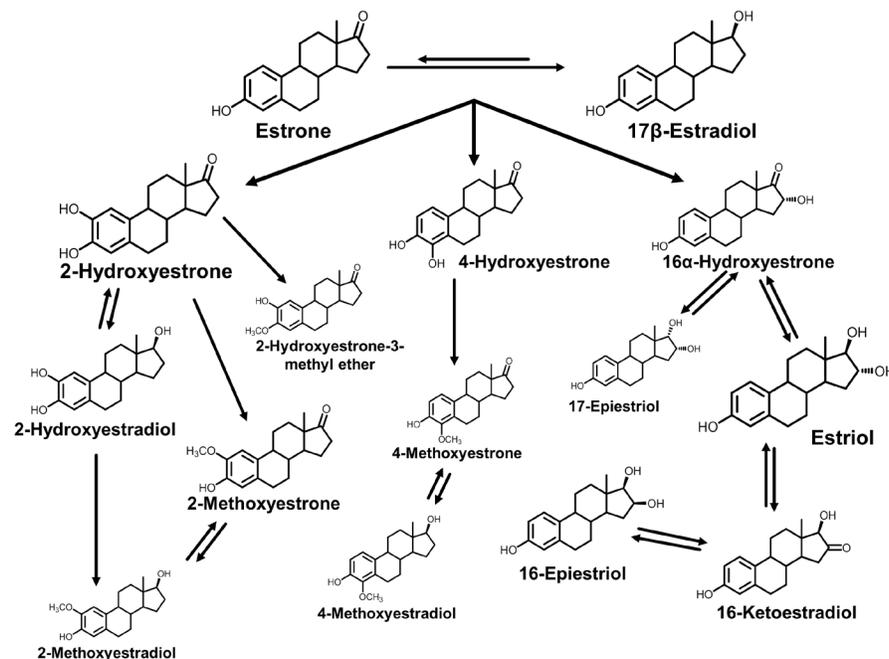
activation of signaling pathways via the estrogen receptor (ER), which leads to altered gene expression and increased proliferation and, in turn, the opportunity for more mutations. The second pathway involves the oxidative metabolism of estrogen (E2/E1) to catechol estrogens and then to reactive quinone metabolites. The quinone metabolites have the ability to form depurinating DNA adducts or to form catechols through the oxidation-reduction cycle that produce reactive oxygen species causing oxidative damage to DNA (Lavigne et al. 2001). The catechols can be inactivated by methylation mediated by catechol-*O*-methyltransferase, glucuronidation, and sulfation. In women, blocking the action of the ER by such agents as tamoxifen, a selective estrogen receptor modulator, or by decreasing estrogen production (e.g., by removing the ovaries in premenopausal women) has been shown to decrease the incidence of breast cancer up to 50% (Fisher et al. 1998; Parker et al. 2009). Estrogen metabolism, which occurs in the liver, kidney, and other organs, including the breast, involves a complex set of pathways (Figure 6.27). Various CYP isoforms, which are often tissue specific, are responsible for the oxidation and conjugation of estrogen metabolites. One of the first steps in estrogen metabolism is the oxidation of the parent estrogens (E2/E1) at the 2, 4, and 16 positions of the carbon skeleton to the 2, 4, and 16 hydroxylated metabolites (Yager and Liehr 1996).

Figure 6.26 Pathways to estrogen carcinogenesis



Source: Adapted from Yager and Davidson 2006, updated for Surgeon General's Report.

Note: 4-OH E1 = 4-hydroxyestrone; 4-OH E2 = 4-hydroxyestradiol; 16α-OH E1 = 16α-hydroxyestrone; E1 = estrone; E2 = estradiol; ER = estrogen receptor.

Figure 6.27 Pathways involved in estrogen metabolism

Source: Adapted from Ziegler et al. 2010.

Davis and colleagues (1993) showed that the 16 hydroxy estrogens exhibit strong estrogenic and mitogenic activities and hypothesized that higher levels of such activities increase the risk for breast cancer by uncontrolled cellular proliferation and by binding to the ER, thereby damaging DNA. The 2- and 4-hydroxy metabolites also exhibit estrogenic activity and can stimulate cellular proliferation. Despite being more abundant than the 4-hydroxy metabolite, the 2-hydroxy metabolite is much less potent and shorter acting. Both the 2- and 4-hydroxy estrogen metabolites can go on to form genotoxic reactive quinone metabolites.

In cell culture studies of granulosa cells, choriocarcinoma cells, and placental microsomes, nicotine was shown to directly inhibit the aromatase enzyme, resulting in reduced conversion of androgens to estrogen in a dose-dependent manner (Barbieri et al. 1986a,b). This is an important pathway, particularly in postmenopausal women among whom estrogen is generated primarily in peripheral tissues. In animal studies, cigarette smoke reduced the number of oocytes, caused toxicity to ovarian follicles, and led to ovarian atresia (Mattison 1982; Blackburn et al. 1994; Miceli et al. 2005), which could affect estrogen production in premenopausal women.

Observational studies have linked cigarette smoking to earlier age at menopause (Baron et al. 1990; Bromberger et al. 1997) and reduced bone density in postmenopausal women (Daniell 1976; Baron et al. 2001); both conditions are associated with relative estrogen deficiency and a reduction in the risk for breast cancer. Smoking is also associated with decreased fertility (USDHHS 2004, 2010) and with earlier menarche in children whose mothers were heavy smokers during pregnancy (Windham et al. 2004); both conditions are known risk factors for breast cancer. However, as noted in the 2001, 2004, and 2010 Surgeon General's reports, the majority of epidemiologic studies comparing circulating endogenous estrogen levels in premenopausal (Table 6.11S) and postmenopausal women (Table 6.12S) have not found differences between smokers and nonsmokers. In several small studies, premenopausal women who smoked were found to have significantly elevated urinary levels of 2-hydroxy E1 or reduced levels of E1, E2, or estriol (E3) during the luteal phase of the menstrual cycle compared with nonsmokers (MacMahon et al. 1982; Michnovicz et al. 1986, 1988; Westhoff et al. 1996). The clinical implications of these findings and any associated changes in breast tissue have not been investigated.

Studies that compared the effect of HRT, an exogenous hormonal exposure, in smokers and nonsmokers did observe differences by smoking status in circulating levels of estrogen and its metabolites, supporting the hypothesis that smoking increases hepatic metabolism of estrogens (Jensen et al. 1985; Jensen and Christiansen 1988; Cassidenti et al. 1990; Geisler et al. 1999). Among postmenopausal women who were using orally administered HRT, circulating estrogen metabolites—including E1, E2, and estrone sulfate—were 40–70% lower in smokers than in nonsmokers (Jensen et al. 1985; Jensen and Christiansen 1988; Cassidenti et al. 1990; Geisler et al. 1999). A dose-dependent, reciprocal increase in the binding capacity of sex-hormone-binding globulin was observed by Cassidenti and colleagues (1990) and, importantly, differences in levels of estrogen and its metabolites were not evident before treatment with HRT in these same women (Jensen et al. 1985; Cassidenti et al. 1990). Furthermore, significant changes in circulating hormone levels between smokers and nonsmokers were not observed after transdermal administration of HRT, a method that bypasses estrogen metabolism in the liver (Geisler et al. 1999; Mueck and Seeger 2005).

Alterations in estrogen metabolism pathways have also been observed in pregnant women who smoked (USDHHS 2001). Several studies have found that pregnant women who smoked had lower levels of circulating E2 and E3 than pregnant women who did not smoke (Targett et al. 1973; Mochizuki et al. 1984; Bernstein et al. 1989; Petridou et al. 1990; Kaijser et al. 2000). However, compared with their nonsmoking pregnant counterparts, rates of 4-hydroxylation were increased in pregnant smokers in samples of placental tissue (Chao et al. 1981; Juchau et al. 1982), and rates of 2-hydroxylation were nonsignificantly increased (Juchau et al. 1982). Smoking did not alter E2 metabolism or the formation of E1, 2-hydroxyestradiol, and other estrogen metabolites, but 15 α -hydroxyestradiol, 4-hydroxyestradiol, and 7 α -hydroxyestradiol were significantly elevated (Zhu et al. 2002). Finally, Piasek and colleagues (2001) found that levels of progesterone were lower in pregnant women who smoked than in those who did not smoke. If the rate of 4-hydroxylation continues to be higher after pregnancy in smokers than in nonsmokers, then smoking may increase risk for breast cancer rather than having a protective effect, as suggested by the anti-estrogenic hypothesis proposed by Michnovicz and colleagues (1986).

Several other circulating hormones have also been compared between smokers and nonsmokers. In premenopausal women, Cramer and colleagues (1994) and Windham and colleagues (2005) did observe higher levels of circulating follicle-stimulating hormone in smokers than in nonsmokers (Table 6.11S). Last, circulating

levels of androgens (e.g., androstenedione, dihydroepiandrosterone sulfate, and testosterone), progesterone, and cortisol have been found to be higher in smokers than in nonsmokers. In postmenopausal women, these elevated levels may affect breast carcinogenesis. Missmer and colleagues (2004) associated increased levels of circulating androgens with increased risk for breast cancer among postmenopausal women. A meta-analysis by Law and colleagues (1997) found that levels of dihydroandrostenedione sulfate and androstenedione were significantly higher in postmenopausal smokers than in nonsmokers but that levels of estrogens did not differ. Finally, cigarette smoking has been shown to directly affect adrenal cortical hormone levels (Baron et al. 1995). The effects of these hormonal changes on breast tissue are not known.

Summary

The available evidence supports biologically plausible mechanisms, particularly for DNA adduct formation and unrepaired DNA mutations, by which exposure to tobacco smoke could cause breast cancer. However, data are limited and a detailed mechanistic model of how exposure to tobacco smoke may affect risk for breast cancer cannot yet be assembled.

Epidemiologic Evidence—Overview

The following sections update and expand the reviews in previous Surgeon General's reports on the associations between cigarette smoking and breast cancer and between exposure to secondhand smoke and breast cancer. Conclusions from previous reports and recent epidemiologic evidence are summarized with reference to the criteria for the assessment of causation used in this series of reports (Hill 1965; USDHHS 2004). The studies reviewed cover a lengthy period of time and include a variety of study designs and inclusion criteria, data collection techniques, exposure measurements, and study endpoints. Reports based on cohort studies prior to 2012 and case-control studies published between 2000–2011 were identified in MEDLINE using key words and extended terms. All studies that evaluated the association between smoking and breast cancer risk and mortality were eligible for review. Combinations of the following key words were used, depending on the evidence sought: breast cancer, breast neoplasms, tobacco smoke, cigarette smoking, active smoking, passive smoke, secondhand smoke, involuntary smoke exposure, case-control study, cohort study, risk, survival, mortality, prognosis, recurrence, second primary, genotype, polymorphism, single nucleotide polymorphisms (SNPs), NAT1, NAT2, CYP1A1 and CYP1B1,

GST, GSTM1, GSTT1, GSTP1, GSTA1, SULT1A1, *MnSOD2*, XRCC1, XPD or ERCC2, MGMT, and *BRCA1*, and *BRCA2*. Additional studies were identified from reference lists in pertinent papers. The search focused on English-language studies that evaluated either (a) the main effects of cigarette smoking or passive exposure to smoke on breast cancer risk or mortality, or (b) the interaction of cigarette smoking or passive exposure to smoke with such risk factors as menopausal status, hormone receptor status, family history, and susceptibility genotypes. All studies that reported a main effect for smoking are identified in the sections below on active smoking (see “Active Cigarette Smoking and Risk for Breast Cancer”) and exposure to secondhand smoke (see “Exposure to Secondhand Smoke and Risk for Breast Cancer”), regardless of whether they were one of multiple studies on the same population. However, when multiple studies were reported for the same population, only the most recent findings, with a few exceptions noted in the analytical sections, were included in the meta-analyses presented later.

Active Cigarette Smoking and Risk for Breast Cancer

Individual authors and various review panels have evaluated the evidence for an association between active and passive cigarette smoking and breast cancer. The first systematic review of such an association was included in IARC Monograph 38 (1986). Based on a review of 10 case-control and 8 cohort studies published between 1959 and 1983, the 1986 IARC monograph found “no consistent effect of smoking on the risk of breast cancer” (p. 298). The literature at the time was limited, however. Only 2 of the case-control studies (CDC 1983; Janerich et al. 1983) were population-based, rather than hospital-based, and few studies adjusted for potential confounders. All but 1 cohort study (Hiatt et al. 1982) mixed incident and decedent cases and few adequately adjusted for relevant confounders. Palmer and Rosenberg (1993) reviewed 5 cohort and 16 case-control studies (9 with population controls, 3 with participants in a screening program, and 4 with hospital controls), finding “little evidence to suggest that cigarette smoking materially increases risk” (p. 154). However, the authors noted that future investigations should consider age at initiation of smoking because of evidence that women were beginning to smoke at earlier ages. Terry and Rohan (2002) published a comprehensive literature review on cigarette smoking and breast cancer, concluding that “the association between cigarette smoking and breast cancer risk remains unclear” and that the observed “increased risk

with smoking of long duration, smoking before a first full-term pregnancy, and passive smoking require (sic) confirmation in future epidemiological studies” (p. 965). They suggested that future studies and meta-analyses consider timing of exposure (e.g., age at initiation of smoking and smoking before first pregnancy), duration and dose (years of exposure and pack-years of smoking), sources of passive exposure, the overlap of active and passive exposures, potential confounders, and modification by menopausal status and genetic susceptibility.

IARC (2004) summarized results from 36 case-control studies, 8 cohort studies, and a large pooled analysis of data from 10 cohort and 43 case-control studies, the pooled analysis having been conducted by the Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002) and based on studies having at least 100 women with incident invasive breast cancer. The pooled analysis was restricted to nondrinkers (38% of cases and 43% of controls), because alcohol was considered a potentially significant confounder of the effects of smoking. Sufficient data were available to consider a wide variety of other potential confounders, including age at diagnosis, parity, age at birth of first child, breastfeeding, race, country, education, family history, age at menarche, height, weight, body mass index (BMI), use of hormonal contraceptives, and menopausal status. Study site, age, parity, and age at first birth were included as covariates in the final analysis of the effect of smoking on risk of breast cancer among nondrinkers. However, the analysis did not consider duration or amount of smoking or exposure to secondhand smoke. Results indicated no association between active smoking and risk for breast cancer (RR = 1.03; 95% CI, 0.98–1.07) in women who did not drink alcohol. The Collaborative Group (2002) also contrasted this result with those for all women regardless of alcohol intake (RR = 1.09) and statistically adjusted for alcohol intake (RR = 1.05). The 2004 IARC report concluded that: (a) the majority of epidemiologic studies “found no association with active smoking, after controlling for established risk factors”; and (b) the Collaborative Group analysis of women who reported themselves to be nondrinkers “confirms the lack of an increased risk of breast cancer associated with smoking” (p. 1183). The Cal/EPA reviewed many of the same studies in 2005 and came to a different conclusion: “Considering the epidemiological studies, the biology of the breast and the toxicology of tobacco smoke constituents together, the data provide support for a causal association between active smoking and elevated breast cancer risk” (p. 7-79).

In April 2009, the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk conducted an extensive descriptive evaluation of active cigarette smoking and exposure to secondhand smoke, paying particular

attention to the timing of these exposures (age at initial exposure and before or during first full-term pregnancy), duration and dose (years of exposure and number of pack-years of smoking), modification by menopausal status, and genetic susceptibility (Collishaw et al. 2009). The panel's approach, to some extent, followed the suggestions of Terry and Rohan (2002) that future studies and meta-analyses focus more carefully on the issues of duration, timing, genetic susceptibility, source of passive exposure, the overlap of passive and active exposure, and potential confounders. The evaluation included summative reviews, meta-analyses, and the most recently published studies through November 2008. Pooled analyses and meta-analyses were not performed. The evaluation paid particular attention to results from the 2002 analysis by the Collaborative Group on Hormonal Factors in Breast Cancer, the 2005 Cal/EPA report, and the 2004 and 2006 Surgeon General's reports.

The Canadian Expert Panel evaluated results from more recent, updated analyses published for four of the cohort studies and nine of the case-control studies that were included in the 2002 Collaborative Report in which duration of smoking was reported. Unlike the 2002 report, which excluded women who consumed alcohol, the Canadian panel reported risk estimates adjusted for alcohol intake. The four cohort studies included the NHS-I (Egan et al. 2002), the Canadian National Breast Screening Study (Cui et al. 2006), the CPS-II (Calle et al. 1994), and the Iowa Women's Health Study (Olson et al. 2005). Three of these (Calle et al. 1994; Olson et al. 2005; Cui et al. 2006) reported significantly increased RRs, ranging from 1.18–1.50, for the longest duration of smoking (≥ 40 years). Among the nine case-control studies (Rohan and Baron 1989; Palmer et al. 1991; Smith et al. 1994; Baron et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002; Alberg et al. 2004; Magnusson et al. 2007; Prescott et al. 2007), five reported an increase in risk of greater than 45% for smoking durations ranging from 11 to more than 50 years and for high cumulative levels of pack-years or cigarette-years³ (Rohan and Baron 1989; Palmer et al. 1991; Johnson et al. 2000; Kropp and Chang-Claude 2002; Alberg et al. 2004). However, results were statistically significant only for postmenopausal women who reported more than 35 years of active smoking (OR = 1.7; 95% CI, 1.1–2.7) in one study (Johnson et al. 2000).

The Canadian Expert Panel also evaluated three cohort studies published after 2002 in which the risk of breast cancer was significantly increased for the longest

durations of active smoking, ranging from 20 or more years to 31 or more years (Al-Delaimy et al. 2004; Reynolds et al. 2004b; Gram et al. 2005). According to the Canadian Expert Panel, when these studies were considered along with three of the four older cohort studies (Egan et al. 2002; Olson et al. 2005; Cui et al. 2006) (Calle et al. 1994 was excluded because it was a mortality study), five reported an increased risk for the highest duration category of smoking: two with borderline significance (RR = 1.15 [95% CI, 1.00–1.33]; 1.18 [95% CI, 1.00–1.38]) (Reynolds et al. 2004b; Olson et al. 2005, respectively) and three with statistical significance (RR = 1.21 [95% CI, 1.01–1.45]; 1.36 [95% CI, 1.1–1.7]; and 1.50 [95% CI, 1.19–1.89]) (Al-Delaimy et al. 2004; Gram et al. 2005; Cui et al. 2006, respectively). However, it should be noted that the result used for the Gram study is based on a subgroup of women who reported ever smoking for at least 20 years. The result for all current smokers with 25 or more years of smoking was increased but not statistically significant (RR = 1.26; 95% CI, 0.98–1.63). Although four of these five studies reported statistically significant trends across levels of duration (Olson did not calculate a p for trend), only three (Gram et al. 2005; Olson et al. 2005; Cui et al. 2006) actually showed unambiguous evidence of an increasing trend with duration of active smoking. The panel also reviewed four cohort studies published after 2002 that reported risk estimates by pack-years of smoking (Reynolds et al. 2004b; Gram et al. 2005; Olson et al. 2005; Cui et al. 2006). Among these studies, three had statistically significant RRs ranging from 1.17–1.48 for the highest category of pack-years (Reynolds et al. 2004b; Gram et al. 2005; Cui et al. 2006). Additionally, the panel reviewed 32 case-control studies in which ORs were reported for duration of active smoking and 27 in which estimates were reported for pack-years. The results from these case-control studies were found to be inconsistent, regardless of menopausal status. The Canadian Expert Panel concluded that the results from the cohort studies for increased risk with longer duration and higher pack-years were more “persuasive” than those from the case-control studies and “that the relationship between active smoking and breast cancer is consistent with causality” (Collishaw et al. 2009, p. 49). Johnson and colleagues (2011) summarized the results from the Canadian Expert Panel in a brief report.

In November 2009, IARC issued a special report on human carcinogens, including tobacco, that encompassed more than 150 epidemiologic studies about the association between tobacco smoke and breast cancer (Secretan

³Cigarette-years: the number of years of smoking multiplied by the number of cigarettes smoked per day.

et al. 2009). This report updated findings and conclusions from the 2004 IARC report and noted that two large cohort studies conducted after 2002 showed positive, but small, statistically significant associations. These studies included the California Teachers Study (hazard ratio [HR] = 1.13; 95% CI, 1.0–1.28) (Reynolds et al. 2004b), which was also reviewed in the 2006 Surgeon General's report, and the Canadian National Breast Screening Study (HR = 1.18; 95% CI, 1.09–1.27) (Cui et al. 2006). Based on these findings and those from previous reports, as well as evidence from studies of animal and human tissues, the IARC panel concluded that “there is limited evidence that tobacco smoking causes breast cancer” (Secretan et al. 2009, p. 1033) and added the female breast as a new cancerous tumor site associated with exposure to tobacco smoking.

In addition to these extensive reports, several reviews and meta-analyses have addressed active cigarette smoking alone (Khuder and Simon 2000; Khuder et al. 2001; Nagata et al. 2006; Ren et al. 2007), exposure to secondhand smoke but not active smoking (Lee and Hamling 2006; Pirie et al. 2008), both active and passive smoking (Morabia 2002b; Johnson 2005; Sadri and Mahjub 2007; Iwasaki and Tsugane 2011), smoking-genotype interactions (Vogl et al. 2004; Masson et al. 2005; Terry and Goodman 2006; Ochs-Balcom et al. 2007; Ambrosone et al. 2008; Zhang et al. 2010), smoking-DNA repair marker interactions (Neumann et al. 2005), timing in relation to first pregnancy or birth of first child (Lawlor et al. 2004; DeRoo et al. 2011b), and intrauterine exposure (Park et al. 2008).

Conclusions from Previous Surgeon General's Reports

The 2001 Surgeon General's report on women and smoking concluded that “active smoking does not appear to appreciably affect breast cancer risk overall,” but it suggested that future research address both age at initiation of smoking and potential susceptibility associated with specific genetic polymorphisms (p. 217). The 2004 Surgeon General's report on the health consequences of smoking evaluated: (a) the influence that cigarette smoking has on endogenous estrogen levels due to changes in metabolism and lowered body weight; (b) the effects of early age at smoking initiation, smoking-genotype interactions, and exposure to secondhand smoke; and (c) carcinogenic and anti-estrogenic effects of smoking on breast tissues.

The 2004 Surgeon General's report concluded that “evidence is suggestive of no causal relationship between active smoking and breast cancer,” that subgroups of women at high risk because of smoking could not be “reli-

ably identified,” and that the previous finding of a lower risk for breast cancer among women with *BRCA1* or *BRCA2* mutations in one study (Brunet et al. 1998) “was not replicated” in a later study (Couch et al. 2001) and therefore not established (USDHHS 2004, p. 312).

The sections below review and quantitatively summarize studies of cigarette smoking by study design (cohort, case-control), and by geographic regions (North America, Europe, Asia) that differ for smoking prevalence, as well as breast cancer incidence and mortality. Table 6.13 shows selected estimates of the prevalence of smoking from the WHO Reports on the Global Tobacco Epidemic (2008a, 2011) for countries represented in these reports. Although there is considerable variation, the prevalence of smoking in women is generally similar in North America and Europe but substantially lower in Asia.

The following sections include reports on the association between smoking and breast cancer risk based on cohort studies published up to 2012 (Table 6.14S) and case-control studies published from 2000–2011 (Table 6.15S). A list of studies by category of exposure is provided in Table 6.16S. Studies based on incident cases that estimate risk of breast cancer are emphasized because studies that focus on mortality may include a different mix of correlates and etiologic pathways affecting survival that alter the association with smoking (Al-Delaimy et al. 2004). As a result, studies of smoking and breast cancer mortality are evaluated in a separate section (see “Exposure to Tobacco Smoke and Breast Cancer Mortality”). Some studies or reviews that mix prevalent with incident cases, however, are included (Lawlor et al. 2004; Hanaoka et al. 2005; Ha et al. 2007).

Cohort Studies

Table 6.14S presents an overview of 15 publications from the 12 cohort studies on breast cancer and active smoking published since 2000 (Manjer et al. 2000b, 2001; Egan et al. 2002; Terry et al. 2002a; Al-Delaimy et al. 2004; Lawlor et al. 2004; Reynolds et al. 2004b; Gram et al. 2005; Hanaoka et al. 2005; Olson et al. 2005; Cui et al. 2006; Ha et al. 2007; Lin et al. 2008; Xue et al. 2011; Luo et al. 2011b). The study by Lawlor and colleagues (2004) was restricted to parous women in the United Kingdom and combined prevalent and incident cases. The report by Manjer and colleagues (2001) was based on the same cohort as used in an earlier report by Manjer and colleagues (2000b), but was restricted to women with tumor tissue available for analysis. Consequently, Lawlor and colleagues (2004) and Manjer and colleagues (2001) are excluded from the meta-analyses and forest plots. Additionally, reports by Terry and colleagues (2002a) and Cui

Table 6.13 Age-standardized estimates of the prevalence of current cigarette smoking for selected member states of the World Health Organization (WHO), 2009

WHO region	Member states	Males (%)	Females (%)
North America	United States	28	24
	Canada	19	16
Europe	Denmark	30	28
	Finland	28	22
	France	36	27
	Germany	33	25
	Italy	33	19
	Netherlands	28	22
	Norway	31	28
	Poland	36	25
	Slovenia	30	22
	Sweden	20	25
	Switzerland	31	21
	United Kingdom	25	23
Western Pacific	Australia	22	19
	China	50	2
	India	11	1
	Japan	42	12
	Republic of Korea	53	6
	Philippines	47	10

Source: Data for Republic of Korea and Sweden are from WHO 2008a (Appendix III, Tables 3.4b and 3.6b). Data for the other member states presented in this table are from WHO 2011 (Appendix VII, Table 7.1.0). Reprinted with permission from World Health Organization, © 2008, 2011.

Note: Prevalence estimates are standardized to age distributions of the country's current smoking. Estimates of current smoking are calculated based on cigarette smoking at the time of survey, daily or nondaily. Estimates rounded to nearest whole number.

and colleagues (2006) were based on the same cohort, the Canadian National Breast Screening Study. Although Table 6.14S summarizes both studies, estimates only from Cui and colleagues (2006) are used in the meta-analyses to avoid duplication. Two reports stem from the NHS-I (baseline year 1976) (Egan et al. 2002; Xue et al. 2011); data from the more recent report are used in the majority of the meta-analyses. Data from the NHS-II are included because it is a separate premenopausal-women-only cohort with a different baseline year (1989) (Al-Delaimy et al. 2004). All three of these studies are summarized in Table 6.14S.

North American Studies

The U.S. Radiologic Technologists Study (USRTS) (Ha et al. 2007) reported nonsignificantly increased RRs for breast cancer among former smokers (RR = 1.17; 95% CI, 0.99–1.38) and current smokers (RR = 1.13; 95% CI, 0.96–1.32). Although the study adjusted for the first year in which an individual worked as a radiologic technician, either residual confounding or synergy may have occurred between smoking and exposure to radiation at work, because previous analyses showed an increased risk (RR =

2.41; 95% CI, 1.32–4.41) associated with exposure to radiation at work among women who were employed before 1940, when exposure to occupational radiation was potentially higher for this group (Mohan et al. 2003; Sigurdson et al. 2003). Eighty-six percent of cases (781 out of 906) were ascertained by self-report, of which 20% (155 out of 781) could not be verified against medical records (Ha et al. 2007), but a previous report from the USRTC indicated 99.4% agreement between self-report and breast cancers ascertained from medical records (Sigurdson et al. 2003). In addition, 14% (125) of the cases were ascertained from death certificates, and date of diagnosis was imputed using the average survival time between 1973 and 2000 based on SEER data.

Several reports from the NHS-I cohort on smoking and breast cancer are based on both premenopausal and postmenopausal women (Willett et al. 1987; London et al. 1989; Hunter et al. 1997; Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002; Egan et al. 2002; Xue et al. 2011). All but two (Egan et al. 2002; Xue et al. 2011) have been incorporated in previous reviews or meta-analyses. The report by Xue and colleagues (2011) analyzed data for 8,772 incident cases of breast cancer in 111,440 women followed for up to 30 years (1976 baseline). The RR was 1.09 (95% CI, 1.02–1.17) for current smokers and 1.06 (95% CI, 1.01–1.11) for former smokers in comparisons with never smokers. These estimates were adjusted for age, family history of breast cancer, age at menarche, height, BMI at 18 years of age, use of oral contraceptives, history of benign breast disease, physical activity, alcohol use, age at first birth, parity, passive smoking at home and at work, current BMI, age at menopause, menopausal status, and use of HRT. Risk was significantly and positively associated with increasing pack-years of smoking (p trend = 0.001), number of cigarettes smoked per day (p trend = 0.02), and duration of smoking (p trend = 0.01), particularly in the intervals between menarche and menopause and menarche and first birth (RR = 1.11; 95% CI, 1.07–1.15; and 1.18; 95% CI, 1.10–1.27 for every 20 pack-years, respectively). The authors also reported a significant trend (p = 0.02) toward decreasing risk with increasing pack-years of smoking after menopause.

In an earlier report from the NHS-I, Egan and colleagues (2002) reported results for a subset of 78,206 premenopausal or postmenopausal women that was restricted to those for whom data on both active and passive smoking were collected and based on an average of 14 years of follow-up (1982 baseline). The RR, based on a reference group of women who reported no history of active or passive smoking, was 1.15 (95% CI, 0.98–1.34) and 1.17 (95% CI, 1.01–1.34) for current and former smokers, respectively. Last, Al-Delaimy and colleagues (2004) analyzed

data from the NHS-II cohort (1989 baseline), based predominantly on premenopausal women, and reported a significantly increased risk for breast cancer among former smokers (RR = 1.18; 95% CI, 1.02–1.36) but not current smokers (RR = 1.12; 95% CI, 0.92–1.37) in comparisons with never smokers over an average of 10 years of follow-up. This study also reported a positive association between risk for breast cancer and increasing duration of smoking (p trend = 0.04) and a significantly increased risk for smoking 20 years or more (RR = 1.21; 95% CI, 1.01–1.45).

Cui and colleagues (2006), using data from the Canadian Breast Screening Study (1980–1985 baseline, 40–59 years of age) reported an increased risk for breast cancer among current smokers (RR = 1.18; 95% CI, 1.09–1.27) but not former smokers (RR = 1.00; 95% CI, 0.93–1.08). This report was an update of the same cohort from an analysis by Terry and colleagues (2002a), but at an average of 16 years of follow up for 4,445 cases rather than an average of 10.6 years for 2,552 cases. Overall, few differences can be found between these two reports. The 16-year follow-up study, using never smokers as the referent, found significant associations between risk for breast cancer and the highest categories of cigarettes smoked per day (RR = 1.20; 95% CI, 1.00–1.44), duration of smoking (RR = 1.50; 95% CI, 1.19–1.89), and pack-years of smoking (RR = 1.17; 95% CI, 1.02–1.34), as well as for smoking for more than 5 years before first pregnancy (RR = 1.13; 95% CI, 1.01–1.25) and for initiation of smoking between 16 and 19 years of age (RR = 1.10; 95% CI, 1.01–1.21). Effect modification by menopausal status was not found, but positive associations were stronger in women who did not report vigorous physical activity.

In the Iowa Women's Health Study cohort, Olson and colleagues (2005) reported a significantly increased risk (vs. never smokers) for breast cancer among postmenopausal current smokers (RR = 1.19; 95% CI, 1.03–1.37) but not former smokers. Increased risks were also detected for age at smoking initiation (older than 18 years of age: RR = 1.11; 95% CI, 1.00–1.24), smoking duration (≥ 40 years: RR = 1.18; 95% CI, 1.00–1.38), and smoking before first pregnancy (RR = 1.21; 95% CI, 1.07–1.37).

Reynolds and colleagues (2004b) used data from the California Teachers Study to evaluate the association of smoking with breast cancer. The authors detected significantly increased risks for breast cancer among current smokers in comparisons with two reference groups: never smokers (RR = 1.32; 95% CI, 1.10–1.57) and women who reported no active or passive exposure to smoking (RR = 1.25; 95% CI, 1.02–1.53). Results for former smokers, when compared with women who reported no active or passive exposure to smoking or with never smokers, were attenuated and not significant, regardless of

reference group. This study reported significant trends toward increasing risk of breast cancer with longer duration and greater pack-years of smoking and more cigarettes smoked per day. In addition, risk of breast cancer was increased in women who initiated smoking before 20 years of age (RR = 1.17; 95% CI, 1.05–1.30) and who smoked for 5 or more years before first pregnancy (RR = 1.13; 95% CI, 1.00–1.28). In response to a letter by Johnson (2004), Reynolds and colleagues (2004a) conducted additional analyses to evaluate the associations for smoking duration, pack-years of smoking, and average number of cigarettes smoked per day with risk of breast cancer stratified by nulliparous women only, parous women who smoked less than 5 years prepartum, and parous women who smoked for 5 or more years prepartum. These analyses suggested a stronger risk effect among parous women who smoked for 5 or more years before first pregnancy for duration, pack-years, and cigarettes smoked per day (RR = 1.12, 1.28, and 1.25, respectively, for highest levels) than for women who smoked for less than 5 years before first pregnancy (RR = 1.18, 1.12, and 1.11, respectively, for highest levels) compared with their nonsmoking counterparts. Results were significant for the highest levels for pack-years and cigarettes smoked per day for parous women who had smoked for 5 or more years prior to pregnancy. Risk of breast cancer was increased among nulliparous women (RR = 1.13, 1.33, and 1.37, respectively, for highest levels), but significant for only those women who reported smoking 20 or more cigarettes per day compared with nonsmoking nulliparous women.

Luo and colleagues (2011b) reported results for 3,520 cases among 79,990 postmenopausal women followed for an average of 10.3 years in the Women's Health Initiative Observational Study cohort. The RRs for former and current smokers were 1.09 (95% CI, 1.02–1.17) and 1.16 (95% CI, 1.00–1.34), respectively, when based on a reference group of never smokers. These risks increased about 7–8% when based on a no active/no passive exposure reference group (RR = 1.16; 95% CI, 0.98–1.38 and RR = 1.24; 95% CI, 1.00–1.54, respectively). Risk was significantly ($p < 0.05$) and inversely associated with age at initiation of smoking, and it was positively associated with cigarettes per day, duration, and pack-years of smoking. The RR for 50 or more pack-years of smoking was 1.18 (95% CI, 1.02–1.37), very similar to the estimate of 1.19 (95% CI, 1.07–1.33) for 51 or more pack-years reported by Xue and colleagues (2011) for the NHS-I. It is important to note, however, that the estimate for the Women's Health Initiative (Luo et al. 2011b) is for postmenopausal women only; the NHS-I (Xue et al. 2011) reported a significant ($p = 0.02$) inverse association with pack-years of smoking after menopause but a strong ($p < 0.001$) positive association before menopause. Thus, these two large cohort stud-

ies provide contradictory results for the effect of smoking on risk of breast cancer in postmenopausal women.

Last, in a companion report from the Women's Health Initiative, Luo and colleagues (2011a) provided results suggesting that the risk of breast cancer is greater in nonobese women who smoke. The RR for current smoking was 1.25 (95% CI, 1.05–1.47) in nonobese women (BMI <30) versus 0.96 (95% CI, 0.69–1.34) in obese women. Significant trends in risk were found for age at initiation, duration and pack-years of smoking, and cigarettes per day in nonobese but not in obese women. The RR for 50 or more years of smoking was 1.62 (95% CI, 1.22–2.17) in nonobese women but only 0.62 (95% CI, 0.28–1.40) in obese women. This is one of three studies to date that have examined the interaction of smoking and body size on risk of breast cancer and the only one to formally test for statistical interaction; the other studies have been case-control. Gammon and colleagues (2004a) also reported an increased risk of breast cancer in lean women (BMI <22.3) exposed to both active and passive smoking (OR = 1.76; 95% CI, 1.06–2.92) but no association for obese women (BMI >29.2) in their case-control Long Island Breast Cancer Study Project. In contrast, Band and colleagues (2002) found a nonsignificant inverse association in ever smokers with a BMI less than 21 (RR = 0.75; 95% CI, 0.29–1.94) but an increased risk in those with a BMI 21 or greater (RR = 1.13; 95% CI, 0.63–2.04); however, the latter result is for lean, normal, overweight, and obese women combined and therefore cannot be compared with the other studies. Luo and colleagues (2011a) speculated as to whether this interaction could be associated with either an anti-estrogenic effect of smoking or with different distributions of genetic susceptibility polymorphisms in obese versus non-obese postmenopausal women.

European Studies

Since 2000, three European cohort reports have been published for findings on two studies of smoking and risk for breast cancer. Gram and colleagues (2005) studied the Norwegian-Swedish Cohort, a large population-based cohort ($n = 102,098$) in Scandinavia with up to 9 years of follow-up. Although the study detected nonsignificant increased risks for breast cancer among former smokers (RR = 1.15; 95% CI, 0.94–1.41) and current smokers (RR = 1.17; 95% CI, 0.95–1.40), it found some strong associations with timing of smoking initiation, duration of smoking, and smoking dose. Risk estimates for initiation of smoking before 15 years of age (RR = 1.48; 95% CI, 1.03–2.13), "before/around menarche" (RR = 1.39; 95% CI, 1.03–1.87), and before first pregnancy (RR = 1.27; 95% CI, 1.00–1.62) were all significantly associated with breast cancer among women who reported smoking for at least 20

years in comparisons with never smokers. Among women with 20 or more years of smoking, significant increased risks were also reported for smoking at least 10 cigarettes per day (RR = 1.34; 95% CI, 1.06–1.70), accumulating 20 or more pack-years of smoking (RR = 1.46; 95% CI, 1.11–1.93), and smoking for at least 25 years (RR = 1.36; 95% CI, 1.06–1.74) in comparison with never smokers. These results were attenuated on the order of 1–7% when analyzed for current smokers and were no longer significant except for pack-years of smoking and number of cigarettes smoked per day, as shown in Table 6.14S. Earlier, Manjer and colleagues (2000b) reported results from a smaller cohort study (n = 10,902) conducted in Malmö, Sweden. In premenopausal and postmenopausal women combined, former smoking—but not current smoking or number of cigarettes smoked per day—was significantly associated with risk for breast cancer (RR = 1.31; 95% CI, 1.02–1.69).

Asian Studies

Since 2000, studies published have included a systematic review of three cohort and eight hospital-based case-control studies by Nagata and colleagues (2006) and a single cohort study by Lin and colleagues (2008). The three cohort studies in the review by Nagata and colleagues (2006) included the study by Hanaoka and colleagues (2005) of middle-aged Japanese women, a study of atomic bomb survivors by Goodman and colleagues (1997), and a study of breast cancer mortality by Hirayama (1984, 1990). All eight case-control studies were conducted before 2000. In addition to multiple problems with the design of these studies, their results are difficult to interpret and have poor generalizability because of the low incidence of breast cancer and very low prevalence of smoking among Asian women (Table 6.13). Although the prevalence of smoking is very low among Chinese women (2%) and low among Japanese (12%) women, it is high among Chinese (50%) and Japanese (42%) men (Table 6.13, based on WHO 2011). Thus, women in Asia are exposed to secondhand smoke more so than to active cigarette smoking.

The study by Lin and colleagues (2008) included approximately 12 years of follow-up of 34,401 women (Table 6.14S). However, the study had limited power to detect an association between smoking and breast cancer because of a small number of cases (n = 208) and the low prevalence of current smoking (1.6%) and former smoking (5.3%). The RRs for breast cancer were 0.67 (95% CI, 0.32–1.38) for current smokers and 1.27 (95% CI, 0.46–3.48) for former smokers. However, when the analysis was restricted to postmenopausal women, current smokers had an elevated, albeit not significant, risk (RR = 1.20; 95% CI, 0.52–2.80). The study included too few premeno-

pausal women to conduct a formal test of interaction, but the results suggest the possibility of effect modification by menopausal status. The Japan Public Health Center-based prospective cohort study by Hanaoka and colleagues (2005) also lacked statistical power, with only 180 incident cases among 21,805 women and a smoking prevalence of 5.7%. Moreover, the analyses appeared to mix incident morbidity data with mortality data. The RRs were 1.7 (95% CI, 1.0–3.1) for current smokers and 1.1 (95% CI, 0.4–3.5) for former smokers, using a no active/no passive reference group. Among premenopausal women, the RR was significantly increased, but imprecisely estimated for ever smokers (RR = 3.9; 95% CI, 1.5–9.9); the study found no increased risk among postmenopausal women (RR = 1.1; 95% CI, 0.5–2.5).

Case-Control Studies

Since 2000, there have been 34 reports based on 30 case-control studies on smoking and breast cancer (Table 6.15S). The reports provided by Metsola and colleagues (2005) and Sillanpaa and colleagues (2005a) were based on the same study group, and both used a no active/no passive exposure reference group. Because the report by Sillanpaa and colleagues (2005a) adjusted for a number of potential confounders and these adjustments made a difference in the reported estimates, this report is used in the meta-analyses and forest plots. Table 6.15S presents an overview of these studies. Seven studies are limited by either a small sample (<200 cases) with low statistical power (Delfino et al. 2000; Morabia et al. 2000; Alberg et al. 2004; Gibson et al. 2010; Kaushal et al. 2010) or by other design features that limit interpretation, such as clinic-based controls (Delfino et al. 2000; Kruk 2007; Cerne et al. 2011) or benign breast disease controls (Delfino et al. 2000). These studies vary considerably in reporting type and detail for measures of smoking and whether results are stratified by ethnicity, menopausal status, or genetic biomarkers.

North American Studies

Since 2000, findings on smoking and risk for breast cancer have been reported across seven large population-based case-control studies with at least 1,000 cases (Johnson et al. 2000; Innes and Byers 2001; Band et al. 2002; Gammon et al. 2004a; Mechanic et al. 2006; Prescott et al. 2007; Slattery et al. 2008; Young et al. 2009). The reports by Fink and Lash (2003) and DeRoo and colleagues (2011a) are not included in this section because they dealt exclusively with smoke exposure during pregnancy. Young and colleagues (2009) conducted the largest case-control study to date, with 6,235 cases and 6,533 controls (Table

6.15S). The study was based on pooled data from two case-control studies in Ontario, Canada: the Ontario Women's Health Study and the Ontario Women's Diet and Health Study. The designs of the two studies were similar, with cases ascertained through the provincial cancer registry and controls randomly selected from a population-based listing or by random-digit dialing. A risk estimate of 1.10 (95% CI, 0.98–1.23) was reported for current smokers versus women with no history of active or passive smoking. A significantly increased risk was found for older age at smoking initiation (≥ 26 years vs. a no active/no passive group) (OR = 1.26; 95% CI, 1.03–1.55), but there were no associations at younger ages of initiation (<12 years: OR = 0.88; 95% CI, 0.59–1.31; 12–15 years: OR = 1.02; 95% CI, 0.90–1.16; 16–20 years: OR = 1.12; 95% CI, 1.01–1.24). There was a significant risk of breast cancer for smoking initiated more than 5 years before first birth (OR = 1.16; 95% CI, 1.04–1.31), and for smoking initiated after first birth (OR = 1.24; 95% CI, 1.02–1.52). These results do not support the hypothesis that early initiation of smoking and smoking before first birth are more strongly associated with risk of breast cancer than are later initiation and initiation of smoking after first birth.

Johnson and colleagues (2000), in a study in eight Canadian provinces, ascertained 2,317 cases through the provincial tumor registries in the mid-1990s. Controls (2,438) were randomly sampled from health plan listings, a property assessment database, or by random-digit dialing. Extensive data were collected via a mailed questionnaire on active smoking and exposure to secondhand smoke. The analyses of cigarette smoking status used two reference groups: never smoker and no active/no passive exposure. Only the no active/no passive exposure referent was used for age at smoking initiation, number of cigarettes smoked per day, duration of smoking, pack-years of smoking, and number of years since quitting smoking. In general, risk estimates were higher when using the no active/no passive referent group than when using the never smoker referent group. Among premenopausal women, adjusted estimates (using no active/no passive as the referent) were higher for former smokers (OR = 2.6; 95% CI, 1.3–5.3) than for current smokers (OR = 1.9; 95% CI, 0.9–3.8); estimates for postmenopausal women were marginally higher for current smokers (OR = 1.6; 95% CI, 1.0–2.5) than for former smokers (OR = 1.4; 95% CI, 0.9–2.1). As for other measures of smoking (using no active/no passive exposure as the referent), premenopausal women had risk estimates at least 20% higher than postmenopausal women for current and former smoking status, age at smoking initiation, number of cigarettes smoked per day, duration of smoking, and number of years since quitting smoking. The study oversampled women younger than 55 years of age, so it is

one of only a few with sufficient statistical power to detect associations among premenopausal women.

Only two studies reported results that were stratified by race/ethnicity. In one, Mechanic and colleagues (2006) provided data from Phases I and II of the Carolina Breast Cancer Study, a study that examined former and current smoking among 894 African American and 1,414 non-Hispanic White women. These cases were ascertained through the North Carolina Central Cancer Registry, and population-based controls ($n = 2,022$) were selected from motor vehicle and Health Care Financing Administration (now the Centers for Medicare & Medicaid Services) listings. This report serves as an update to the study by Marcus and colleagues (2000), which provided age and race-adjusted estimates from Phase I. In the study by Mechanic and colleagues (2006), risk for breast cancer was significantly increased in African American women who were former smokers (OR = 1.80; 95% CI, 1.30–2.50) or who had smoked more than 20 years (OR = 1.80; 95% CI, 1.20–2.60). In contrast, risk was not significantly elevated for White women who were former smokers (OR = 1.20; 95% CI, 0.90–1.50) or who had smoked for more than 20 years (OR = 1.10; 95% CI, 0.90–1.50). Increased risk was not significantly associated with current smoking for either racial group.

Slattery and colleagues (2008) conducted a population-based case-control study in Arizona, Colorado, New Mexico, and Utah. This study provided data on the risk of breast cancer associated with smoking status, pack-years of smoking, age at smoking initiation, and smoking before first pregnancy. Among women with a first primary breast cancer who had data for smoking, 798 were Hispanic/American Indian and 1,527 were non-Hispanic White. Cases were ascertained from state or national cancer registries (e.g., NCI's SEER Program). Population-based controls were randomly sampled, of which 924 Hispanics/American Indians and 1,601 non-Hispanic Whites had data for smoking. Among premenopausal non-Hispanic White women, risk for breast cancer was significantly increased among ever smokers (OR = 1.3; 95% CI, 1.0–1.7), those who smoked before first pregnancy (OR = 1.4; 95% CI, 1.0–1.9), and those who accumulated more than 15 pack-years of smoking (OR = 1.6; 95% CI, 1.1–2.4). The study did not find any significant associations with breast cancer in premenopausal Hispanic and American Indian women or in postmenopausal non-Hispanic White or Hispanic/American Indian women.

Results from the three remaining large case-control studies are inconsistent. Gammon and colleagues (2004a), who reported results from the Long Island Breast Cancer Study Project for 1,356 cases and 1,383 population-based controls, found that risk for breast cancer was not significantly increased among active/current smokers using a

no active/no passive exposure referent regardless of the number of cigarettes per day, pack-years of smoking, age at smoking initiation, or smoking before first pregnancy. Significant associations were not found in a variety of subgroups, even after stratifying by menopausal status, BMI, alcohol use, use of HRT, use of oral contraceptives, family history, and age at reference date. In Los Angeles, Prescott and colleagues (2007), who conducted a case-control study of 1,728 cases and 441 controls, did not find significant associations between risk for breast cancer and smoking status, duration of smoking, age at smoking initiation, or smoking before first pregnancy. In contrast, Band and colleagues (2002) reported significant associations between risk for breast cancer and ever smoking (OR = 1.50; 95% CI, 1.09–2.07) and smoking for at least 20 years or more (OR = 1.60; 95% CI, 1.08–2.37) in premenopausal but not postmenopausal women based on responses from 1,018 cases and 1,025 controls who participated in a study conducted in British Columbia, Canada. There were no significant associations between risk and age at smoking initiation, but smoking before first pregnancy was significant for premenopausal women (OR = 1.51; 95% CI, 1.07–2.13) but not for postmenopausal women.

Six additional but smaller studies (<1,000 cases) that were conducted in the United States are notable for their findings (Lash and Aschengrau 2002; Egan et al. 2003; Li et al. 2005; Rollison et al. 2008; Ahern et al. 2009; Brown et al. 2010). In one, Li and colleagues (2005) examined a sample of 975 cases and 1,007 controls in Washington state and found a significantly increased risk (30% in each instance) for breast cancer among ever smokers, those who smoked, those 20–39 years of age, those who started smoking before age 20, and those who smoked before their first full-term birth. In addition, women who reported 20 or more pack-years of smoking and a history of HRT involving both estrogen and progestin had increased risk for breast cancer. The study by Lash and Aschengrau (2002) stands out because it found a significant inverse association for ever smoking (OR = 0.72; 95% CI, 0.55–0.95). That 2002 study conflicts, however, with a 1999 study (OR = 2.0; 95% CI, 1.1–3.6) in the same geographic area of Cape Cod, Massachusetts, carried out by the same team (Lash and Aschengrau 1999). Both studies included deceased cases and controls for which information about smoking was collected from proxies. However, the 2002 study, unlike the 1999 study, did not provide information about the fraction of data collected from proxy respondents. Thus, the results of the 2002 study could have been affected by information bias.

In a report from the Collaborative Breast Cancer Study, a population-based study conducted in Maine, Massachusetts, New Hampshire, and Wisconsin between 1988–1991 (Baron et al. 1996), Egan and colleagues (2003)

analyzed data from the Massachusetts and Wisconsin sites (791 cases, 797 controls) for effect modification of smoking risk by *NAT2* genotype. Not accounting for genotype, this study found a significantly increased risk for ever smokers (OR = 1.37; 95% CI, 1.12–1.69) and for women with more than 25 pack-years of smoking (OR = 1.54; 95% CI, 0.87–2.71). Results for the latter variable were OR = 1.54 (95% CI, 0.87–2.71) for premenopausal women and OR = 1.53 (95% CI, 1.10–2.13) for postmenopausal women. In a subsequent report, Ahern and colleagues (2009) analyzed data from only the Massachusetts site in the Collaborative Breast Cancer Study (557 cases, 432 controls) but did not find an association between pack-years of active smoking (OR = 0.90; 95% CI, 0.7–1.3 for >23 pack-years) and risk of breast cancer. However, this report was focused mainly on effects or associations with passive smoking.

The study by Rollison and colleagues (2008) reported an increased risk for breast cancer among ever smokers (OR = 1.43, 95% CI, 1.03–1.99). The authors attempted to compare results based on a no active/no passive to a no active-only reference group but the sample size was too small to provide sufficient statistical power to make an evaluation. Brown and colleagues (2010) conducted a case-control study of risk factors for breast cancer among Asians (Chinese, Filipino, Japanese) who immigrated to San Francisco-Oakland, California; Los Angeles, California; or Oahu, Hawaii. Just over one-half of the women in the study (54% of cases; 58% of controls) were born in Asia (China, Taiwan, Hong Kong, Macau, Japan, the Philippines, Southeast Asia, the Malaysian Peninsula, Singapore, or India) as opposed to Western or Western-style countries (such as those in North America or Europe or the nations of Australia and New Zealand). Women born in Asia and more recent migrants (<8 years) to the West had a lower risk of breast cancer regardless of smoking history than women born and raised in the West or a Western-style country. The overall OR for ever smoking was 1.2 (95% CI, 0.9–1.6). The only significant association between smoking and breast cancer was for age at initiation of younger than 16 years of age (OR = 2.92; 95% CI, 1.1–7.9), but this was based on a very small stratum (11 cases, 9 controls).

European Studies

Since 2000, three large (>1,000 cases) population based case-control studies have been conducted in Europe: one each in Germany (Andonova et al. 2010; Rabstein et al. 2010), Sweden (Magnusson et al. 2007), and Poland (Lissowska et al. 2006). Andonova and colleagues (2010) reported results from the Gene Environment Interaction and Breast Cancer in Germany (GENICA) study that included estimates of risk for breast cancer for former (OR = 0.95; 95% CI, 0.75–1.19) and current (OR =

0.84; 95% CI, 0.66–1.06) smoking using data for 1,021 cases and 1,015 controls in the greater Bonn region. This report and a companion report (Rabstein et al. 2010) were restricted to those subjects with available DNA and are further described in the section on genetic susceptibility.

Magnusson and colleagues (2007) ascertained 3,345 cases from six regional cancer registries and randomly selected 3,454 controls from a governmental population listing in Sweden. The study found few significant or consistent associations between risk of breast cancer and current or former smoking, duration of smoking, pack-years of smoking, age at initiation of smoking, or smoking before first full-term birth. However, data were missing for nearly 17% of cases and 25% of controls. The higher rate of missing data in controls was due partly to the use of a telephone interview that did not collect data for alcohol consumption and perhaps other covariates. In the Polish study, Lissowska and colleagues (2006) did not obtain significant results for all women considered together. However, among women younger than 45 years of age ($n = 511$), significantly increased risks were observed for current smoking (OR = 2.03; 95% CI, 1.40–2.95), the highest level of duration of smoking (>20 years: OR = 2.33; 95% CI, 1.32–4.13), smoking before first pregnancy (OR = 2.03; 95% CI, 1.40–2.94), and ever smoking approached statistical significance (OR = 2.40; 95% CI, 1.00–5.72). It is difficult to interpret some of these associations due to conflicting findings across levels of these exposures; for example, risks were also increased for duration of smoking less than 10 years (OR = 1.57; 95% CI, 1.01–2.44) and for smoking after first pregnancy (OR = 2.40; 95% CI, 1.27–4.53). Kruk (2007) also conducted a clinic-based study in Poland in which the control group was characterized by a higher prevalence of smoking than those in the general population. This study found some of the highest significant risks to date among women who smoked 10 or more cigarettes per day. Here, the ORs were 2.55 (95% CI, 1.81–3.60) for premenopausal women and 1.78 (95% CI, 1.33–2.37) for postmenopausal women.

In England, Roddam and colleagues (2007) conducted a population-based study of 639 cases, 36–45 years of age, with 640 age-matched controls. Significant associations were not detected for former smokers (OR = 1.15; 95% CI, 0.87–1.53) or current smokers (OR = 1.04; 95% CI, 0.79–1.36), age at initiation of smoking, duration of smoking, or number of cigarettes smoked per day. Data for duration of smoking and age at smoking initiation were analyzed as continuous variables. Thus, the results were not combined with those from other studies in generating summary estimates. The OR for former smokers, when calculated using a no passive/no active exposure reference group, was slightly lower (OR = 1.12; 95% CI, 0.72–1.73)

for women with no passive exposure, and it decreased a bit more for women reporting passive exposure (OR = 1.09; 95% CI, 0.75–1.56). Interpreting the importance of the differences among the various estimates is difficult because none are statistically significant and the CIs overlap. Kropp and Chang-Claude (2002) evaluated the same smoking measures with a no active/no passive reference group. Their estimate for former smokers was comparable to that of Roddam and colleagues (2007) but was considerably higher for current smokers (OR = 1.47; 95% CI, 0.99–2.20). Last, Cerne and colleagues (2011) reported results from a clinic-based case-control study of breast cancer among 784 cases and 709 controls among postmenopausal Slovenian women. This report was focused on the effects of HRT, but an estimate was provided for smoking at least 10 cigarettes per day, adjusting for age and education only (OR = 1.70; 95% CI, 1.20–2.43). Notably, the reference group of nonsmokers included former smokers.

Asian Studies

Two small case-control studies from Asia were published between 2000 and 2011. For ever smoking, the study conducted in Manila, the Philippines (Gibson et al. 2010), reported an RR of 1.3 (95% CI, 0.6–2.9), and a study in northeast India (Kaushal et al. 2010) reported an RR of 1.15 (95% CI, 0.62–2.13).

Adjustment for Selected Covariates

Breast cancer is recognized as a heterogeneous disease with many associated risk factors (Hankinson and Hunter 2001; Brinton et al. 2002; Spicer and Pike 2005; Hortobagyi et al. 2006). Some of these risk factors have complex relationships with cancer of the breast, and the direction of their associations may differ according to characteristics such as breast cancer phenotype, age, menopausal status, and race/ethnicity. Established risk factors include:

- increasing age;
- family history of breast cancer in first-degree relatives;
- increased levels of endogenous estrogen;
- history of benign breast disease;
- mammographically dense breasts;
- less frequent screening;

- history of ionizing radiation exposure to the chest;
- various reproduction-related factors—increased risk with younger age at menarche (<12 years of age), older age at menopause (>54 years of age), older age at first pregnancy or live birth (>30 years of age), no history of breast feeding or a short duration of lactation, nulliparity, and decreased risk with increased number of pregnancies;
- higher socioeconomic status (e.g. higher level of education and/or family income);
- use of exogenous hormones (HRT, combined estrogen/progesterone oral contraceptives); and
- increased body size among postmenopausal women (as determined by height, weight, BMI, waist circumference, waist/hip ratio).

Studies have also demonstrated a modestly increased risk for breast cancer, on the order of 25–30%, associated with low level of physical activity (Friedenreich and Cust 2008) and on the order of nearly 50% with intake of 45 or more grams of alcohol per day (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002; Baan et al. 2007). IARC (2002) has concluded that alcohol consumption is a causal risk factor for breast cancer; additionally, Volume 6 of the *IARC Handbook on Cancer Prevention* concluded that regular physical activity reduces the risk of breast cancer. Many of these factors show a complex pattern of association that depends on timing in relation to other exposures, specifically increased estrogen levels, duration of exposure, and menopause. Differences in the distributions of these factors between women who smoke and those with no history of active smoking are likely to vary across populations; to the extent possible, the potential for confounding has been considered in individual studies and in the meta-analyses.

The great majority of cohort and case-control studies published since 2000 and described in this report (Tables 6.14S and 6.15S) either adjusted for, or evaluated the need for adjustment of, relevant confounders. Reproductive factors and family history are well-established, strong risk factors for breast cancer (Spicer and Pike 2005). In addition, since 2000 an increasing number of studies have demonstrated that alcohol use and obesity are important risk factors for breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002). In a review by Kendall and colleagues (2007), the authors found that higher BMI is associated with increased endogenous estradiol levels among postmenopausal women. Although they did not find a clear relationship between alcohol use and

estrogen levels, there was an apparent positive trend with increasing alcohol consumption (Kendall et al. 2007). All cohort studies described in this report adjusted for at least one reproductive factor and BMI; most of them either adjusted for or stratified on menopausal status; and all but one adjusted for alcohol consumption (Lawlor et al. 2004). Three cohort studies (Table 6.14S) did not adjust for family history (Manjer et al. 2000b; Lawlor et al. 2004; Gram et al. 2005).

The selection of covariates for adjustment varied across case-control studies (Table 6.15S). Some studies did not adjust for reproductive factors (Delfino et al. 2000; Alberg et al. 2004; Li et al. 2005; Metsola et al. 2005), alcohol intake (Delfino et al. 2000; Zheng et al. 2002b; van der Hel et al. 2003b; Alberg et al. 2004; Metsola et al. 2005), body size (Delfino et al. 2000; van der Hel et al. 2003b; Alberg et al. 2004; Metsola et al. 2005; Mechanic et al. 2006; Prescott et al. 2007), or family history (Johnson et al. 2000; van der Hel et al. 2003b; Alberg et al. 2004; Li et al. 2005; Metsola et al. 2005; Slattery et al. 2008). Five case-control studies did not adjust, stratify, or match on menopausal status, but in these studies the age range included both premenopausal and postmenopausal women (Marcus et al. 2000; Lash and Aschengrau 2002; Alberg et al. 2004; Metsola et al. 2005; Magnusson et al. 2007). Several studies explored models that adjusted for multiple covariates but reported results for only the most parsimonious models, adjusting for covariates that changed point estimates on the order of 5–15% (Marcus et al. 2000; van der Hel et al. 2003b; Gammon et al. 2004a; Li et al. 2005; Lisowska et al. 2006; Mechanic et al. 2006; Kruk 2007; Magnusson et al. 2007; Rollison et al. 2008; Young et al. 2009). Most studies with findings that were considered for inclusion in the meta-analyses made an effort to statistically detect and adjust for confounders within the data. However, the methods for considering potential confounders varied across studies and the basis for selecting the final, adjusted model was not always explicit.

Meta-Analysis of Breast Cancer Risk Associated with Measures of Active Smoking

All available non-overlapping cohort study reports published prior to 2012 and case-control study reports published from 2000–2011 were included in meta-analyses for this report. These timeframes were selected to identify the most recent evidence that was specifically relevant to associations between risk for breast cancer and active and passive smoking. The older literature has been repeatedly reviewed; the majority of studies published before 2000

were either cross-sectional or case-control in design and were not considered for inclusion in the meta-analysis. Reports from cohort studies published prior to 2000 were evaluated for inclusion; most of these have been superseded by subsequent reports. Table 6.16S provides a listing of the 65 reports from case-control and cohort studies. Twenty-six reports overlapped with results on the same study population, and of these, 11 were included in the meta-analyses because they were either the most recent or complete reports from their study. In the case of 1 cohort study (NHS-I) and 1 case-control study (Collaborative Breast Cancer Study), 2 reports contributed to separate meta-analyses because they offered different measures (NHS-I: Egan et al. 2002 and Xue et al. 2011; Collaborative Breast Cancer Study: Egan et al. 2003 and Ahern et al. 2009). Three cohort studies (Mills et al. 1989b; Land et al. 1994; Thomas et al. 1997), which were included in the report by the Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002), were excluded from the present report because the individual estimates were not published in the original reports and they were combined into an 'other' category for the Collaborative Report. Four studies (1 cohort, 3 case-control) were included in only the meta-analysis of smoking before a first full-term pregnancy or first birth (Innes and Byers 2001; Fink and Lash 2003; Lawlor et al. 2004; DeRoo et al. 2011a). Thus, a total of 46 separate reports were included in the initial analysis of ever smoking. The total number included in each subsequent meta-analysis depended on whether a risk estimate was reported in a study for the measure of smoking. RR estimates were pooled across categories of exposure to fit common definitions of ever smoking, smoking status (former or current), duration of smoking, cigarettes smoked per day, pack-years of smoking, age at smoking initiation, and smoking before first pregnancy. Data are provided in Table 6.16S on studies affected by design and analysis issues, including small sample size, a mixed reference group (former smokers and nonsmokers combined), inadequate covariate adjustment, use of proxy subject reports, issues associated with exposure category cutpoints, and the presence of extreme outliers.

The DerSimonian and Laird (1986) procedure for random-effects meta-analysis was used to calculate summary estimates. The random-effects model was selected because the studies included in the meta-analysis showed substantial variation in type and quality of design, time period, geographic setting, composition of population, ascertainment of cases, selection of controls for case-control studies, and definition and measurement of smoking exposure. Whereas a fixed-effects model assumes that all studies are estimating the same true effect and that

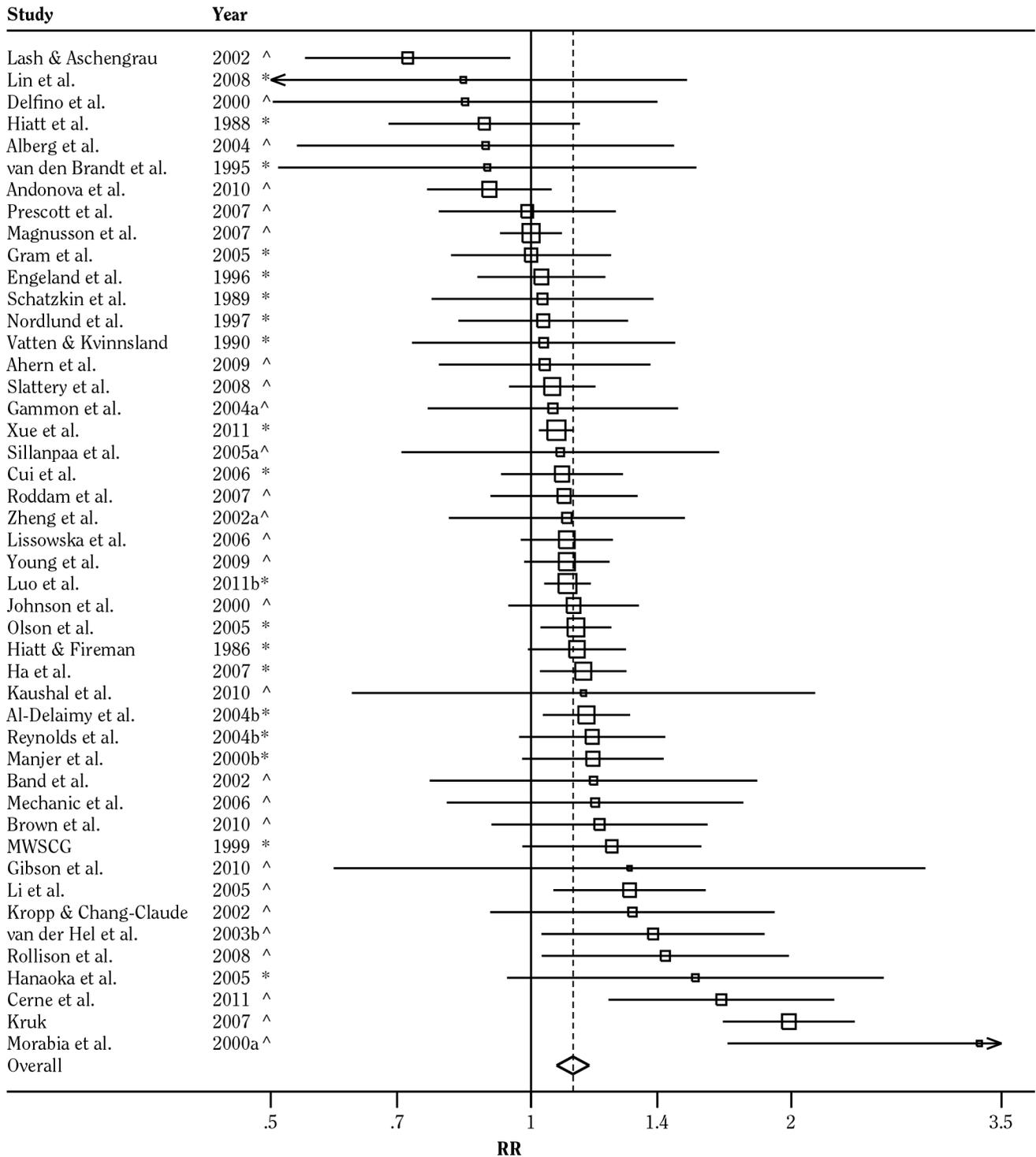
differences between studies are the result of random variation (precision) within studies, a random-effects model assumes that between-study variation is partly due to factors that influence the magnitude of the *true* effect within each study, resulting in a distribution of true effects across studies. The fixed-effects model gives greater weight to larger, more precise studies, whereas the random-effects model dampens to some degree the influence of these larger studies relative to smaller ones. Additionally, the summary estimates from random-effects models generally have broader CIs than those from fixed-effects models, making the former method intrinsically more conservative (Borenstein et al. 2009). The random-effects model accounts for heterogeneity among studies, which can be quantified, for example, in the Q-test statistic. When heterogeneity is low, the random-effects model converges with the fixed-effects model.

Meta-analyses were conducted in STATA 11.0 (STATA Corp., College Station, TX, USA) using the meta STATA command (Sterne 2009). The meta-funnel STATA command was used to create funnel plots for visual assessment of publication bias and outliers. Between-study heterogeneity was assessed with Cochran's χ^2 test, reported as the Q-test statistic, and bias was assessed formally using Egger's statistical test (Egger et al. 1997) and Begg's rank correlation test (Begg and Mazumdar 1994), with the latter calculated via the metabias STATA command. The Begg test is reported to have low power when the number of studies is small. The Egger test is more powerful but also biased and can produce false-positive results (Deeks et al. 2005). Sensitivity analyses considered study design, prevalence of exposure, sample size, and measurement of exposure effect. Results for the Begg and Egger tests are included as a note in figures as appropriate. Summary estimates from random effects models are reported for all meta-analyses.

Ever Smoking

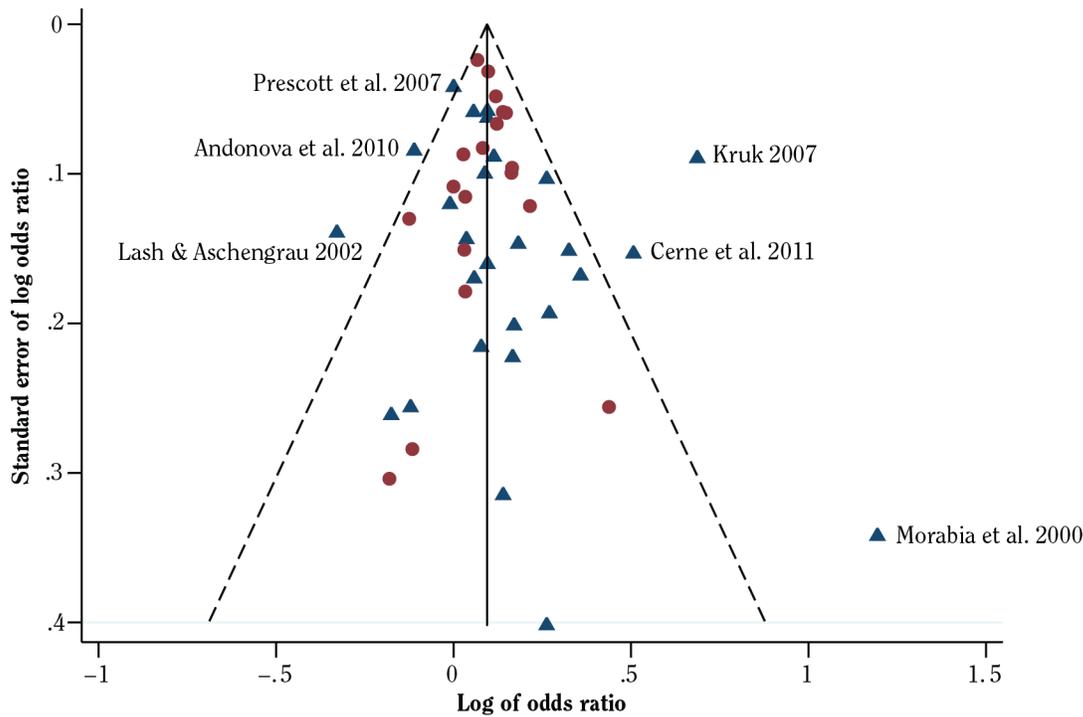
If not reported, a measure for ever smoking was calculated for all 46 studies by pooling available data on smoking status, smoking duration, cigarettes smoked per day, or pack-years of smoking, with the exception of four studies that provided data only for exposure before or during first pregnancy (Table 6.16S). A meta-analysis was conducted of nonoverlapping reports from all cohort studies through 2011, as well as case-control studies published from 2000–2011, for ever smoking, resulting in a summary estimate with significant heterogeneity ($p_h < 0.001$): RR = 1.12 (95% CI, 1.07–1.17; $n = 46$) (Table 6.17S, Figure 6.28). From visual inspection, the funnel plot in Figure 6.29 shows no sign of skewness, indicating that publica-

Figure 6.28 Forest plot showing association between ever smoking and risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 46)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.12 (95% CI, 1.07–1.17); Begg z = 0.48, p = 0.63; Egger bias = 0.44, p = 0.25. See Table 6.17S (note a) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **MWSCG** = Million Women Study Collaborative Group; **RR** = relative risk.

Figure 6.29 Funnel plot for estimates in meta-analysis of ever smoking with risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 46)



Note: l = cohort study; p = case-control study. Includes the same studies reported in Figure 6.28.

tion bias was not a significant issue. This finding was further confirmed by Begg's rank correlation test ($z = 0.48$, $p = 0.63$) and the Egger test (bias = 0.44, $p = 0.25$). Stratification by study design revealed that the heterogeneity was due primarily to variation among the 27 case-control studies (RR = 1.15; 95% CI, 1.06–1.25; $p_h < 0.001$) than to variation among the 19 cohort studies (RR = 1.10; 95% CI, 1.07–1.13; $p_h = 0.793$).

Thirteen studies were excluded in the following sequence (some studies fell into more than one category).

1. Six cohort studies reported in the pooled analysis restricted to nondrinkers conducted by the Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002) and for which there were no data available on smoking in the original report (van den Brandt et al. 1995; Engeland et al. 1996; Million Women Study Collaborative Group 1999).
2. Eight additional studies, three cohort (Schatzkin et al. 1989; Hanaoka et al. 2005; Lin et al. 2008) and five case-control (Delfino et al. 2000; Morabia et al.

2000; Alberg et al. 2004; Gibson et al. 2010; Kaushal et al. 2010), with less than 210 cases.

3. Two additional studies, one cohort (Vatten and Kvinnsland 1990) and one case-control (Cerne et al. 2011), with an estimate reported for only current smokers and for which the reference group appeared to mix never smokers with former smokers.

The summary estimate for the 12 cohort studies remaining (Table 6.17S) after the exclusion of the 7 studies that were restricted to nondrinkers had a small sample, or a mixed reference group did not change meaningfully from the overall estimate (RR = 1.10; 95% CI, 1.07–1.13; $p_h = 0.717$). For case-control studies, the RR was attenuated slightly (RR = 1.13; 95% CI, 1.04–1.23; $p_h < 0.001$) when 6 were excluded that were either small (<210 cases), from Asia, or had a mixed reference group (Table 6.16S). The additional exclusion of a cohort study (Nordlund et al. 1997) that adjusted only for age and place of residence did not alter the summary RR for cohort studies. The funnel plot in Figure 6.29 indicates that the studies by Kruk

(2007) and Lash and Aschengrau (2002) are outliers. The case-control study by Lash and Aschengrau (2002) relied on proxy interviews for deceased cases. Kruk (2007), which was conducted in Poland, used clinic-based controls that were reported to have a higher percentage of smoking (33%) than in the general population (23%). However, a comparison of self-reported prevalence of cigarette smoking and cotinine saliva samples (cutpoint for active smoking—1.5 nanogram [ng]/milliliter [mL]) indicated that true prevalence may be underestimated in Poland by 4.4% (West et al. 2007). The removal of Kruk (2007) and Lash and Aschengrau (2002) resulted in a summary risk estimate of 1.08 (95% CI, 1.03–1.13) and decreased heterogeneity ($p_h = 0.340$) for case-control studies, without adding significant bias according to the Begg ($z = 0.73$, $p = 0.46$) and Egger (bias = 0.43, $p = 0.19$) tests (see notes for Figure 6.30). The RR for the combined case-control and cohort studies ($n = 30$) decreased to 1.09 (95% CI, 1.06–1.12; $p_h = 0.500$). In summary, the significant heterogeneity among studies for the association between ever smoking and breast cancer is attributable mainly to the study by Kruk (2007), which is the more extreme of the two outliers. Excluding this study substantially reduces heterogeneity and results in an attenuated summary estimate. When taken together, these 30 studies suggest that ever smoking increases the RR for breast cancer by a statistically significant average of 9% (Table 6.17S, Figure 6.30). These 30 reports remained as the baseline to be considered for the remaining meta-analyses.

No Active-Only Versus No Active/No Passive Exposure Referent Group

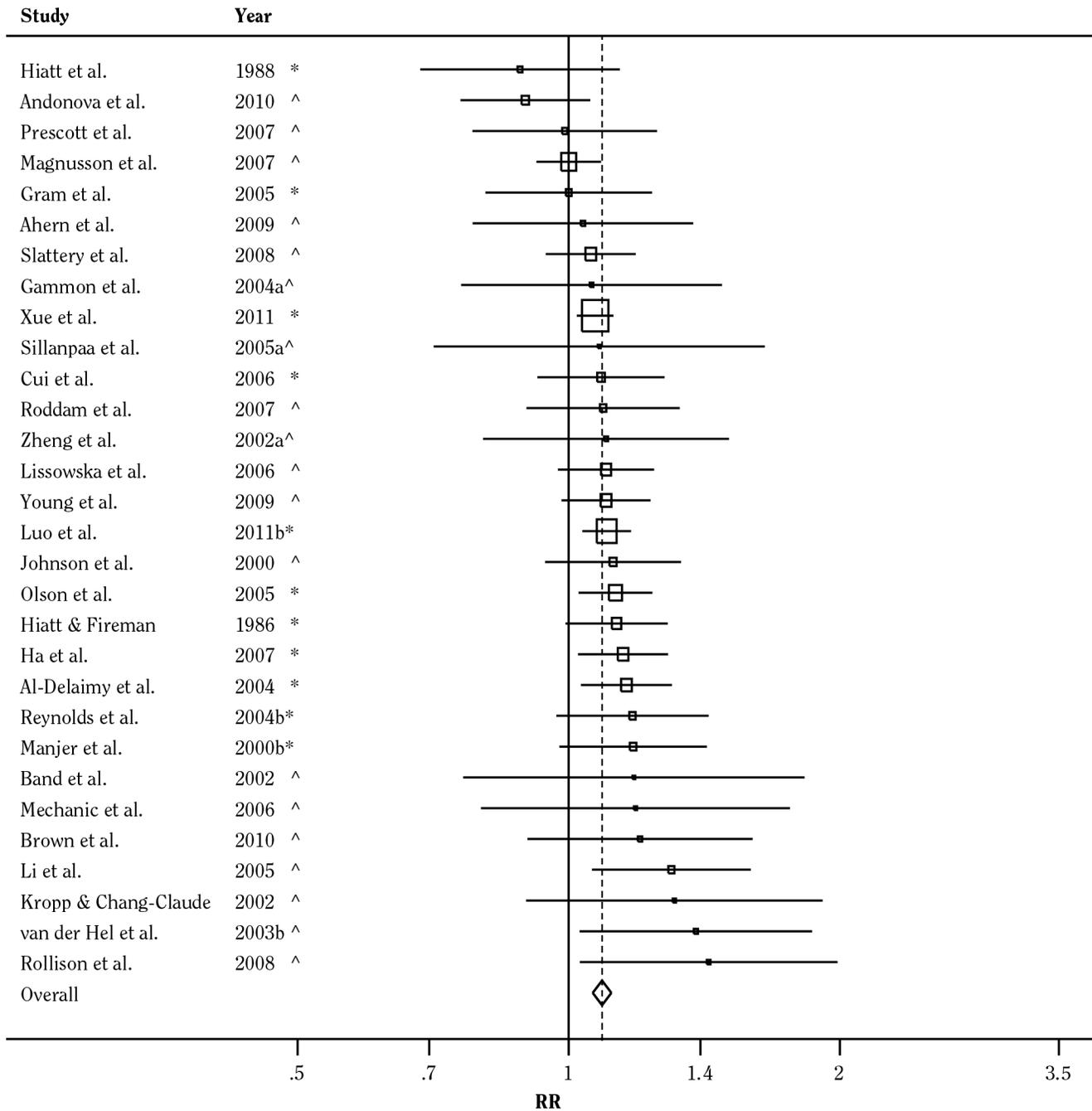
Wells (1991) first suggested that the most appropriate reference group would exclude women who were exposed to passive smoke because their inclusion would attenuate the association with active smoking. Morabia and colleagues (1996) first used this criterion in an analysis of data from a case-control study in Switzerland. Since then, other investigators have narrowed the definition of the reference group to women who report no active or passive smoking exposure. In this report, 5 cohort studies (Egan et al. 2002; Reynolds et al. 2004b; Gram et al. 2005; Hanaoka et al. 2005; Luo et al. 2011b) and 14 case-control studies (Morabia et al. 2000; Delfino et al. 2000; Johnson et al. 2000; Kropp and Chang-Claude 2002; Lash and Aschengrau 2002; Alberg et al. 2004; Gammon et al. 2004a; Sillanpaa et al. 2005a; Lissowska et al. 2006; Mechanic et al. 2006; Roddam et al. 2007; Rollison et al. 2008; Ahern et al. 2009; Young et al. 2009) included results based on a no active/no passive exposure reference group. Ten studies reported results for both reference groups that can be compared for ever smoking (Johnson

et al. 2000; Egan et al. 2002; Reynolds et al. 2004b; Gram et al. 2005; Hanaoka et al. 2005; Lissowska et al. 2006; Roddam et al. 2007; Rollison et al. 2008; Ahern et al. 2009; Luo et al. 2011b). Six compared estimates using the two referent groups by smoking status (Johnson et al. 2000; Egan et al. 2002; Reynolds et al. 2004b; Hanaoka et al. 2005; Roddam et al. 2007; Luo et al. 2011b), 1 did so by pack-years (Ahern et al. 2009), and 2 provided comparisons by duration, dose, and timing (Rollison et al. 2008; Luo et al. 2011b). Nine studies used only a no active/no passive reference group (Delfino et al. 2000; Morabia et al. 2000; Kropp and Chang-Claude 2002; Lash and Aschengrau 2002; Alberg et al. 2004; Gammon et al. 2004a; Sillanpaa et al. 2005a; Mechanic et al. 2006; Young et al. 2009). As noted previously, estimates for ever smoking were derived for some studies by pooling other exposure measures, such as former and current smoking. Additionally, the terminology for defining these reference groups (no active-only, no active/no passive) varies among studies, although the definitions are common.

The size of the reference group is greatly decreased when restricted to no active/no passive exposure because of the high prevalence of passive smoking exposure: most studies indicate that only about 10–20% of never smokers report no passive exposure. In a study by Arheart and colleagues (2008), an estimated 28% of people who reported no passive exposure were actually exposed based on serum cotinine levels, suggesting that the true no active/no passive group may be even smaller, particularly if considered in a lifetime context. No systematic analyses have been conducted to determine whether using only a small no active/no passive referent produces selection bias or sparse data bias (Greenland et al. 2000) as well as loss of statistical power, or whether statistical adjustment for passive smoking exposure in assessing active smoking is as efficient as having a no active/no passive referent. One exception may be Ahern and colleagues (2009), who estimated associations of active smoking with breast cancer using a restricted no active/no passive exposure reference group while also employing statistical adjustment for passive smoking exposure. Unfortunately, it is difficult to interpret the differences between the two approaches because only 30% of participants in that study had data for both active and passive smoking.

In the California Teachers Study cohort (Table 6.14S), the RRs for breast cancer in current smokers overall were both significant and quite similar with the two reference groups used: no active-only (“never”) (RR = 1.32; 95% CI, 1.10–1.57) and no active/no passive (RR = 1.25; 95% CI, 1.02–1.53) (Reynolds et al. 2004b). In contrast, ORs for ever smokers (i.e., former or current) in Johnson and colleagues’ (2000) population-based

Figure 6.30 Forest plot showing association between ever smoking and risk for breast cancer, based on cohort studies published before 2012 and case-control studies published from 2000 to 2011, excluding studies with design or analysis issues (n = 30)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.09 (95% CI, 1.06–1.12); Begg z = 0.73, p = 0.46; Egger bias = 0.43, p = 0.19. See Table 6.17S (note c) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Canadian case-control study were 1.0 (95% CI, 0.8–1.3) for premenopausal women and 1.2 (95% CI, 1.0–1.4) for postmenopausal women when based on the no active-only (“never”) reference group, versus 2.3 (95% CI, 1.2–4.5) for premenopausal women and 1.5 (95% CI, 1.0–2.3) for postmenopausal women when based on the no active/no passive exposure reference group. Although these results seem to suggest a strong effect when using a no active/no passive exposure reference group, the estimates were based on a restricted subgroup of women (62% of the reference group) who were able to account for and report data for more than 90% of their lifetime residential passive smoking exposure. In addition, the no active/no passive reference group consisted of only 193 women (49 premenopausal and 144 postmenopausal women), compared with 2,292 women in the no active-only reference group.

Only two case-control studies have compared results for measures of smoking other than ever smoking or smoking status, but the results are difficult to interpret because of small samples and low statistical power (Rollison et al. 2008; Ahern et al. 2009). For cohort studies, Lin and colleagues (2008) compared results using the two different definitions of reference groups (no active/no passive, no active-only) in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk and stated there was no difference in the estimates, but they did not provide numerical evidence. Luo and colleagues (2011b) reported findings for the only cohort study to date with parallel, multivariable adjusted analyses contrasting no active/no passive exposure with no active-only reference groups for multiple measures. The use of a no active/no passive exposure reference group resulted in a small but consistent increase in RR ranging from 2–10% for most measures of active smoking (ever, status, age at initiation, duration, cigarettes smoked per day, pack-years). The strongest effect of active smoking was for duration greater than 50 years, where the RR was 1.45 (95% CI, 1.06–1.98) using a no active/no passive exposure group compared with 1.35 (95% CI, 1.03–1.77) using a no active-only (“never”) reference group. The analysis suggests that the use of a no active/no passive exposure reference group may provide a small benefit in control for confounding between active and passive smoking effects. However, this small gain in control of confounding is at the cost of statistical power. It has not been established whether statistical adjustment for passive exposure of estimates for the risk of active smoking adequately controls for this confounding. Additionally, the small, restricted subgroup with no active/no passive exposure could differ systematically for other confounders or modifiers that are not measured or adequately controlled. Luo and colleagues (2011b) did not systematically compare the subgroup of no active/no passive smokers with the rest of the

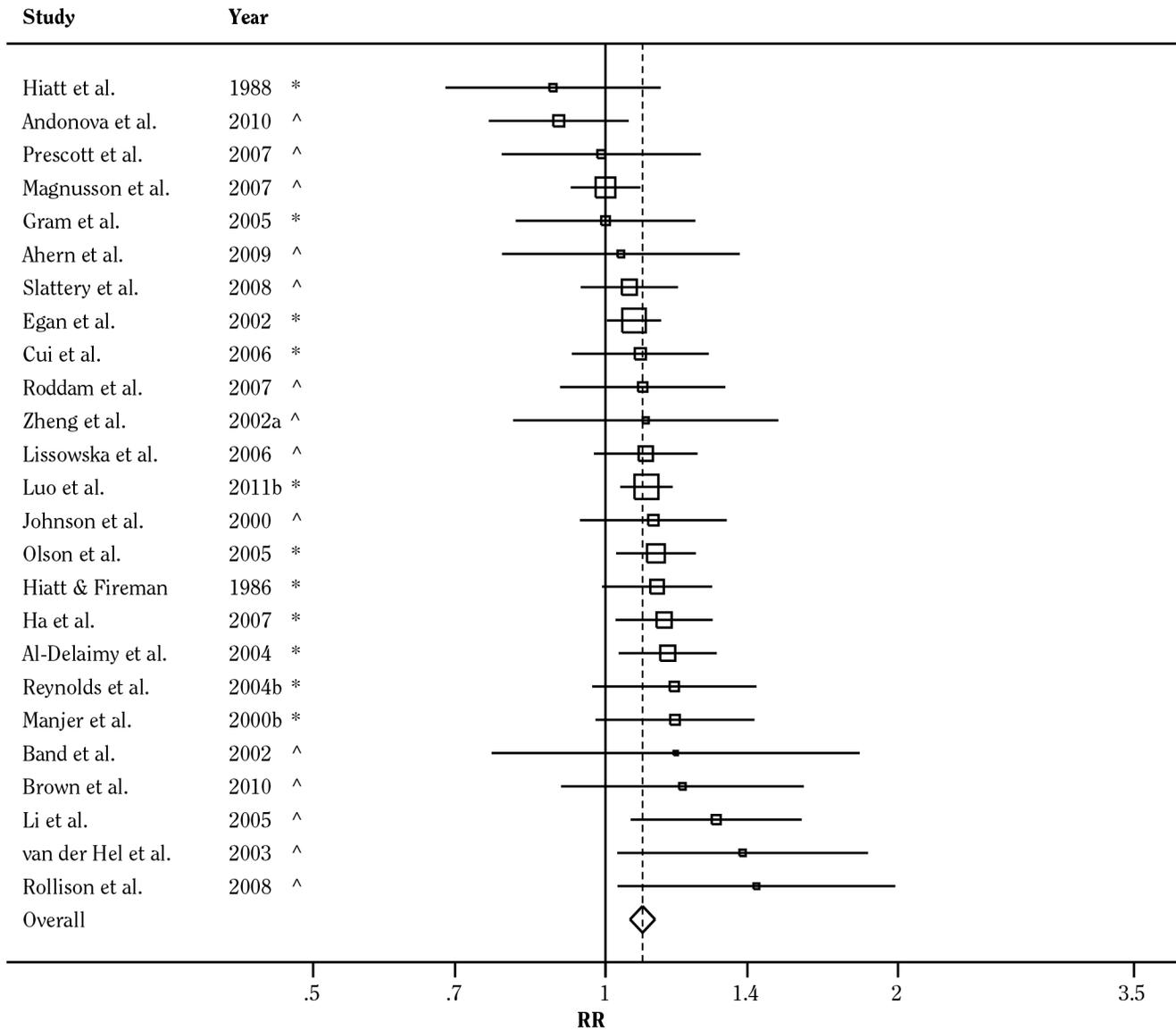
study population to determine whether there were any differences for other potential confounders such as race/ethnicity, education, alcohol consumption, or reproductive variables. This comparison, in fact, was not made in any of the studies that used a no active/no passive exposure reference group.

Meta-analyses were conducted to compare 27 studies reporting results based on a no active-only reference group with 15 studies reporting estimates based on a no active/no passive exposure reference group (Table 6.16S), after the 13 exclusions cited previously. The number of studies was further reduced to 25 for the no active-only and 14 for the no active/no passive exposure analyses with the exclusion of 3 studies (Nordlund et al. 1997; Lash and Aschengrau 2002; Kruk 2007) for reasons given above. The report by Egan and colleagues (2002) was used because the more recent report by Xue and colleagues (2011) did not report results using a no active/no passive exposure reference group. The RR for the no active-only exposure reference group was 1.09 (95% CI, 1.06–1.13; $p_h = 0.308$) (Table 6.17S, Figure 6.31). This estimate is slightly lower than that calculated for 14 studies using a no active/no passive exposure reference group (RR = 1.15; 95% CI, 1.09–1.21; $p_h = 0.572$) (Table 6.17S, Figure 6.32). Nine of the studies—4 of which were large cohort studies (Egan et al. 2002; Reynolds et al. 2004b; Gram et al. 2005; Luo et al. 2011b)—calculated estimates using both reference groups. These 9 studies were included in the two meta-analyses. Neither of these analyses was significantly affected by publication or small-study bias, according to Begg or Egger statistics (see notes for Figures 6.31 and 6.32; funnel plots not shown). These analyses suggest that the use of a restricted no active/no passive exposure reference group results in a small increase in estimates of the association between ever smoking and breast cancer.

Cigarette Smoking Status

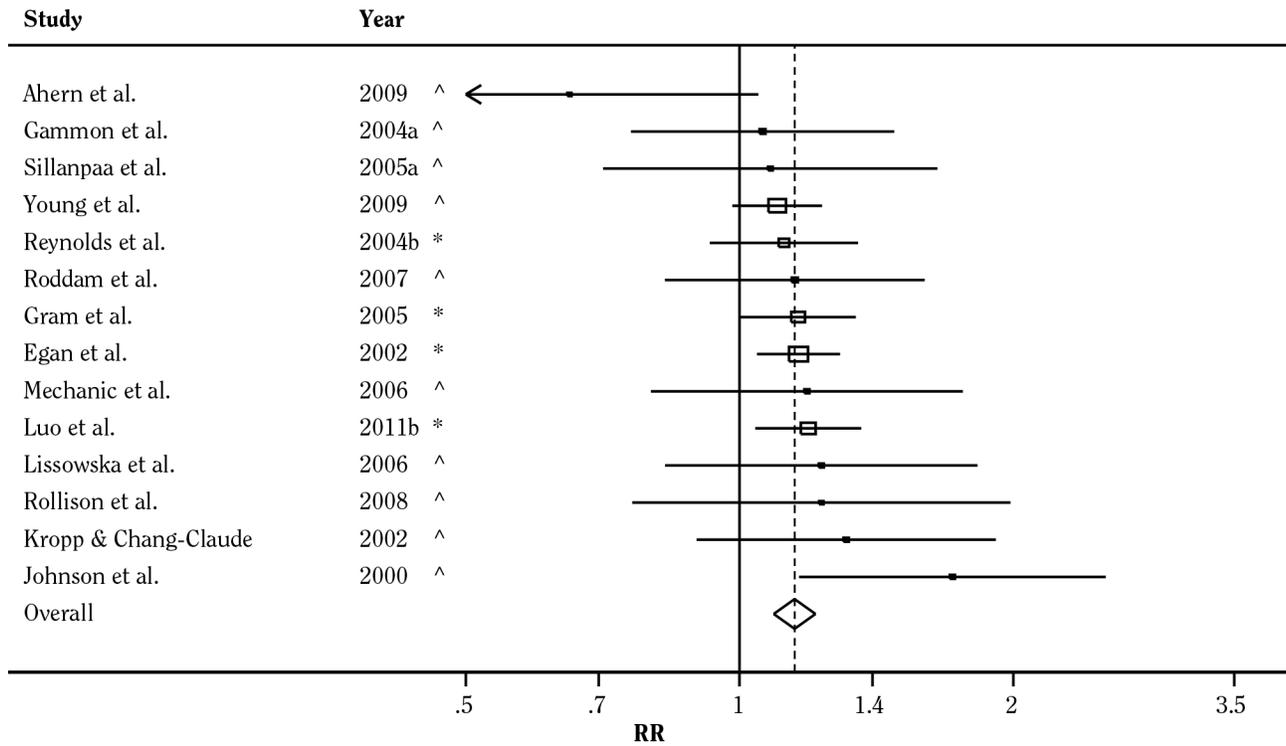
A total of 25 studies reported estimates for current and former smoking; 20 used a no active-only and 5 a no active/no passive exposure reference group (Table 6.16S, Figures 6.33 and 6.34). The summary estimates were similar for current smokers (RR = 1.12; 95% CI, 1.08–1.16; $p_h = 0.347$) and former smokers (RR = 1.09; 95% CI, 1.05–1.13; $p_h = 0.062$) (Table 6.17S). Results for former smokers were virtually identical for the two study designs: cohort (RR = 1.09; 95% CI, 1.03–1.14; $p_h = 0.021$) and case-control (RR = 1.09; 95% CI, 1.03–1.16; $p_h = 0.354$). The summary estimate for current smokers in the 11 cohort studies (OR = 1.14; 95% CI, 1.10–1.18; $p_h = 0.746$) was higher than the estimate for those in the 14 case-control studies (OR = 1.07; 95% CI, 1.00–1.16; $p_h = 0.209$). Sensitivity analyses were conducted that excluded the 4 case-control studies (Kropp and Chang-Claude 2002; Gammon

Figure 6.31 Forest plot showing association between ever smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 with a no active-only referent group (n = 25)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.09 (95% CI, 1.06–1.13); Begg z = 0.70, p = 0.48; Egger bias = 0.43, p = 0.34. See Table 6.17S (note d) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Figure 6.32 Forest plot showing association between ever smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 with a no active/no passive exposure referent group (n = 14)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.15 (95% CI, 1.09–1.21); Begg z = 0.05, p = 0.96; Egger bias = 0.04, p = 0.94. See Table 6.17S (note e) for studies excluded. There were nine studies with estimates reported for both a no active-only and a no active/no passive reference group (also shown in Figure 6.31). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. CI = confidence interval; RR = relative risk.

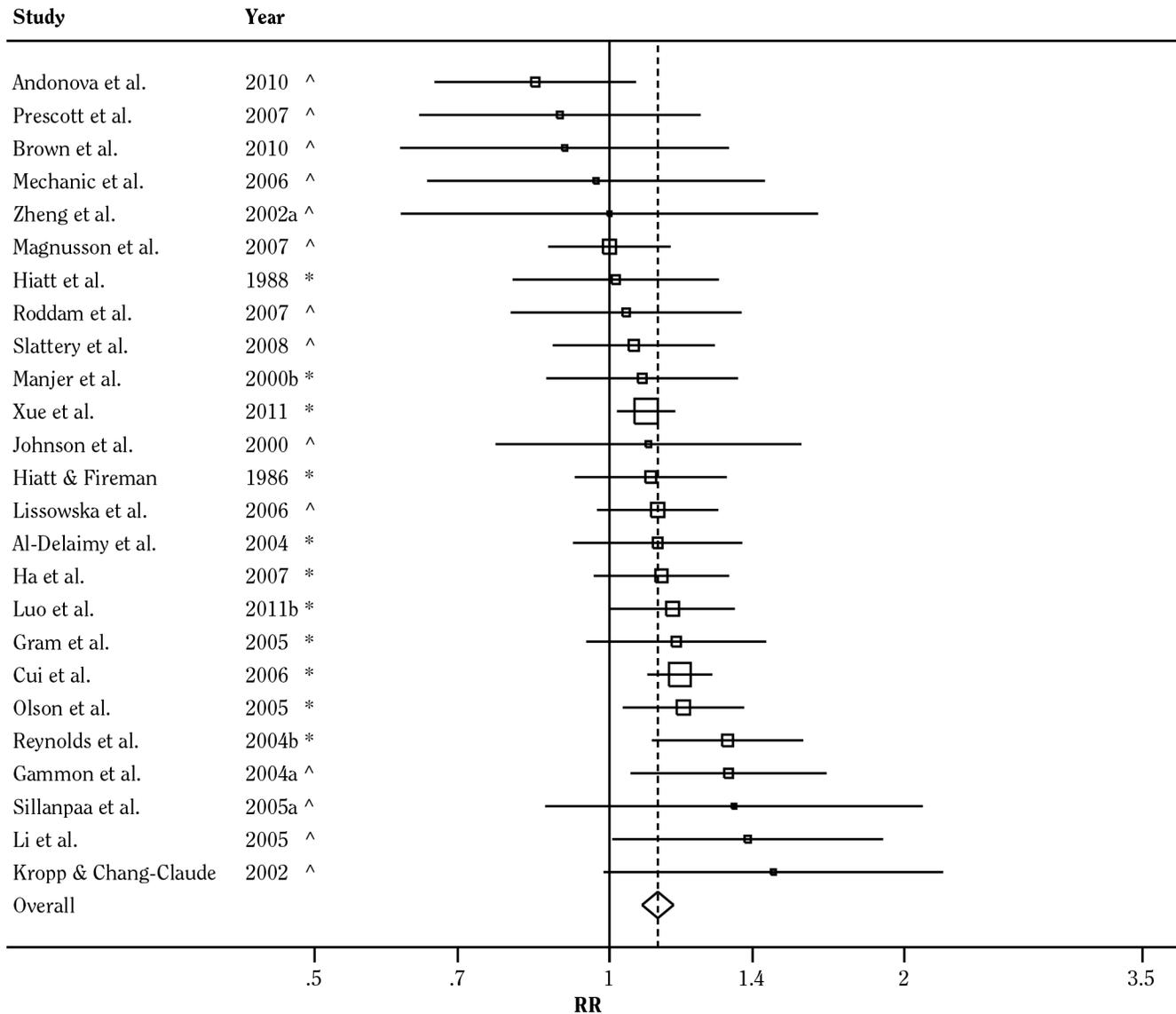
et al. 2004a; Sillanpaa et al. 2005a; Mechanic et al. 2006) and 1 cohort study (Gram et al. 2005) with estimates based on only a no active/no passive exposure reference group. Excluding these studies did not meaningfully alter the overall results for either current smokers (RR = 1.11; 95% CI, 1.07–1.16) or former smokers (RR = 1.09; 95% CI, 1.04–1.13). There was significant heterogeneity among the cohort studies for the association with former smoking because of 1 study (Hiatt et al. 1988) with an outlying estimate (RR = 0.65; 95% CI, 0.47–0.89). The exclusion of this study, as well as the other 5 that were excluded, eliminated the heterogeneity ($p_h = 0.220$) but did not change the point estimate. The association between risk for breast cancer and former smoking may be attenuated relative to current smoking because the former association includes women with variable lengths of time since cessation. These results suggest that current smoking is

associated with an increase in the RR for breast cancer by an average of 12%, and former smoking with an increase by an average of 9%. These results are similar to those for ever smoking. Neither of these analyses was significantly affected by publication or small-study bias according to Begg or Egger statistics (see notes for Figures 6.33 and 6.34).

Duration of Cigarette Smoking

Several cohort studies support an association between risk for breast cancer and long duration of smoking exposure (Table 6.14S). The Canadian National Breast Screening Study (RR = 1.50; 95% CI, 1.19–1.89; p trend = 0.0003 for ≥ 40 years) (Cui et al. 2006) and the NHS-II (RR = 1.21; 95% CI, 1.01–1.45; p trend = 0.04 for ≥ 20 years) (Al-Delaimy et al. 2004) both showed

Figure 6.33 Forest plot showing association between current smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 25)

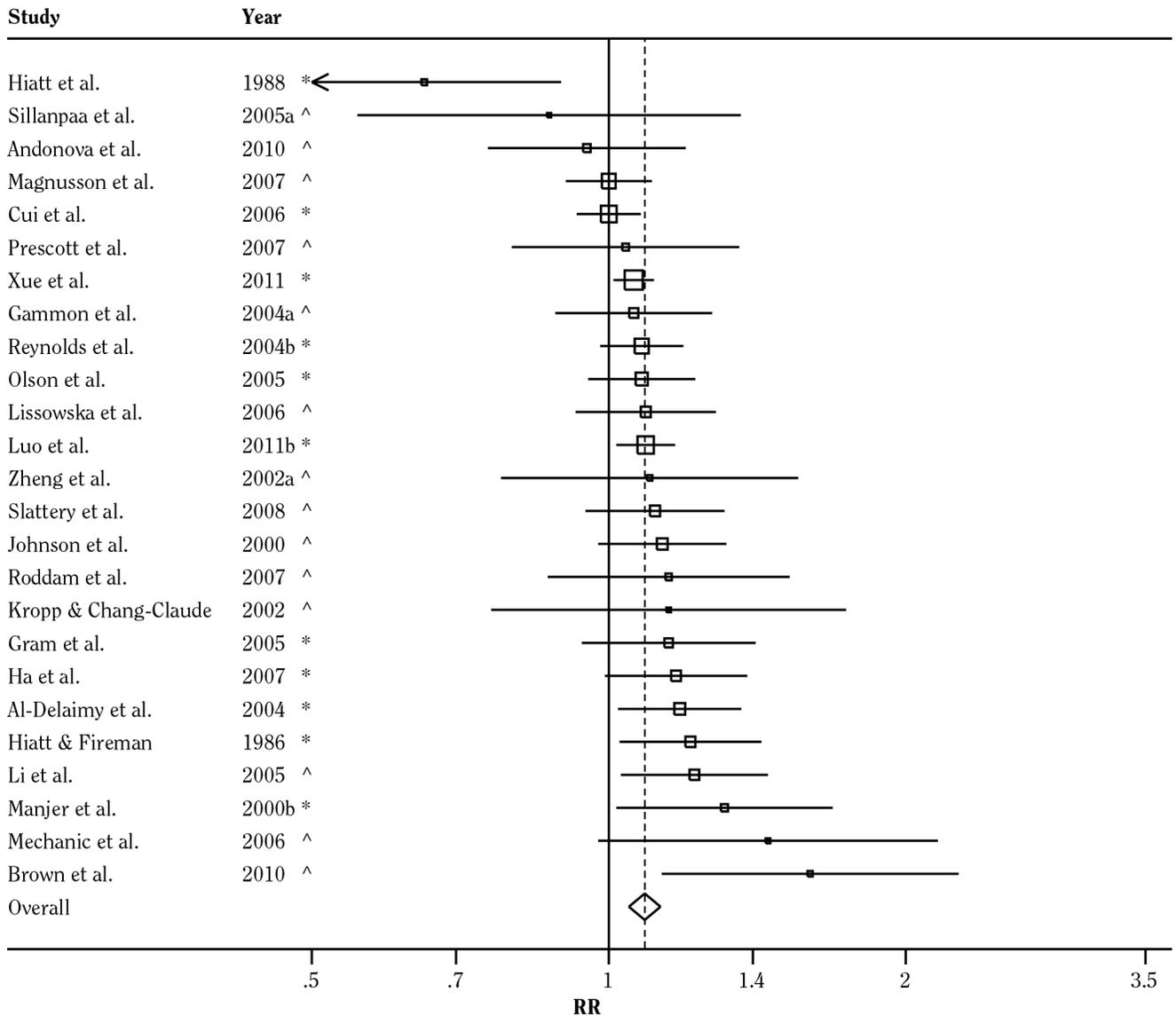


Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.12 (95% CI, 1.08–1.16); Begg z = -0.75, p = 0.46; Egger bias = -0.21, p = 0.62. See Table 6.17S (note f) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

increased risks that were significant at approximately 16 and 10 years of follow-up, respectively. An earlier analysis of the Canadian cohort by Terry and colleagues (2002a) showed risk to be approximately 7% higher for 40 or more years of smoking (RR = 1.61; 95% CI, 1.19–2.19; p for trend = 0.009), but the 2002 report was based on 1,893

fewer cases than that of the report by Cui and colleagues (2006). The two analyses adjusted for the same covariates. Although Egan and colleagues (2002) did not observe a significant trend for the association between risk for breast cancer and duration of smoking (p for trend = 0.18) in the NHS-I, the recent updated analysis by Xue and

Figure 6.34 Forest plot showing association between former smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 25)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.09 (95% CI, 1.05–1.13); Begg z = 0.96, p = 0.34; Egger bias = 0.58, p = 0.19. See Table 6.17S (note f) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. CI = confidence interval; RR = relative risk.

colleagues (2011) with 30 years of follow-up found a significant trend (p = 0.01). The RRs were 1.04, 1.07, and 1.15 for <20, 20–39, and 40 or more years of smoking, respectively. Luo and colleagues (2011b) reported a highly significant (p trend = 0.0002) increased risk with duration of smoking in the Women’s Health Initiative, with an RR of 1.35 (95%

CI, 1.03–1.77) at the highest level (≥50 years). Because all of these studies adjusted for age, it is difficult to attribute these trends to confounding by that variable.

In response to comments posed by Johnson (2004) about analyses of the California Teachers Study data (Reynolds et al. 2004b), Reynolds and colleagues

(2004a) presented essentially the same results for all women (RR = 1.15; 95% CI, 1.00–1.33; *p* trend = 0.009 at ≥ 31 years of smoking duration) and for nulliparous women only (RR = 1.13; 95% CI, 0.84–1.52; *p* trend = 0.081, also at ≥ 31 years of duration). Two other cohort studies showed increased risks of 26% (Gram et al. 2005) and 18% (Olson et al. 2005), respectively, for the highest categories of smoking duration.

A total of 21 studies reported estimates for duration of smoking, after the 13 exclusions cited above (Table 6.16SA and B) (Roddam et al. 2007) not included because only continuous result reported. Nineteen studies with data for smoking duration of 20 or more years have examined the associated risk for breast cancer and were included in the meta-analysis: 7 cohort (Al-Delaimy et al. 2004; Reynolds et al. 2004b; Gram et al. 2005; Olson et al. 2005; Cui et al. 2006; Luo et al. 2011b; Xue et al. 2011) and 12 case-control studies (Johnson et al. 2000; Band et al. 2002; Kropp and Chang-Claude 2002; Zheng et al. 2002a; van der Hel et al. 2003b; Li et al. 2005; Lissowska et al. 2006; Mechanic et al. 2006; Magnusson et al. 2007; Prescott et al. 2007; Rollison et al. 2008; Brown et al. 2010) (Table 6.16S, Figure 6.35). The summary estimate (RR) for these studies was 1.16 (95% CI, 1.12–1.21; $p_h = 0.318$) (Table 6.17S). The Egger test was significant, but the Begg test was not, and thus this result may be influenced by publication or small-study bias (see note for Figure 6.35). The summary estimate (RR) was 1.15 (95% CI, 1.10–1.19; $p_h = 0.819$) for the 7 cohort studies and 1.23 (95% CI, 1.12–1.36; $p_h = 0.146$) for the 12 case-control studies (Table 6.17S). Three case-control studies had cutpoints that were greater than 20 years (Zheng et al. 2002a; van der Hel et al. 2003b; Magnusson et al. 2007), and the reference group in 1 cohort (Gram et al. 2005) and 3 case-control studies was based on no active/no passive exposure (Johnson et al. 2000; Kropp and Chang-Claude 2002; Mechanic et al. 2006). A sensitivity analysis that excluded these 7 studies resulted in similar overall summary estimates for all studies (RR = 1.15; 95% CI, 1.11–1.19; $p_h = 0.43$), case-control (RR = 1.21; 95% CI, 1.05–1.40), and cohort studies (RR = 1.14; 95% CI, 1.10–1.19).

The same analyses were conducted to estimate the summary RR for less than 20 years of smoking duration to compare it with the result for 20 years or more. The summary estimate for the 19 studies was 1.04 (95% CI, 1.01–1.07) (Table 6.17S). There was no evidence of publication or small-study bias according to Begg's or Egger's statistics ($p > 0.05$). There was no difference in the RR between case-control and cohort studies, and the estimate was not attenuated with the exclusion of studies using a no active/no passive reference group or those that had a cutpoint that differed by more than 2 years from the 20 years

of duration used in the meta-analyses. This indicates an increasing trend in risk with longer duration of smoking or a dose-response relationship. These results suggest that active smoking of long duration (i.e., 20 or more years) increases risk for breast cancer by a significant average of 15%. This estimate may be conservative, as some studies indicate that risk continues to increase with smoking over longer periods (Cui et al. 2006; Luo et al. 2011b).

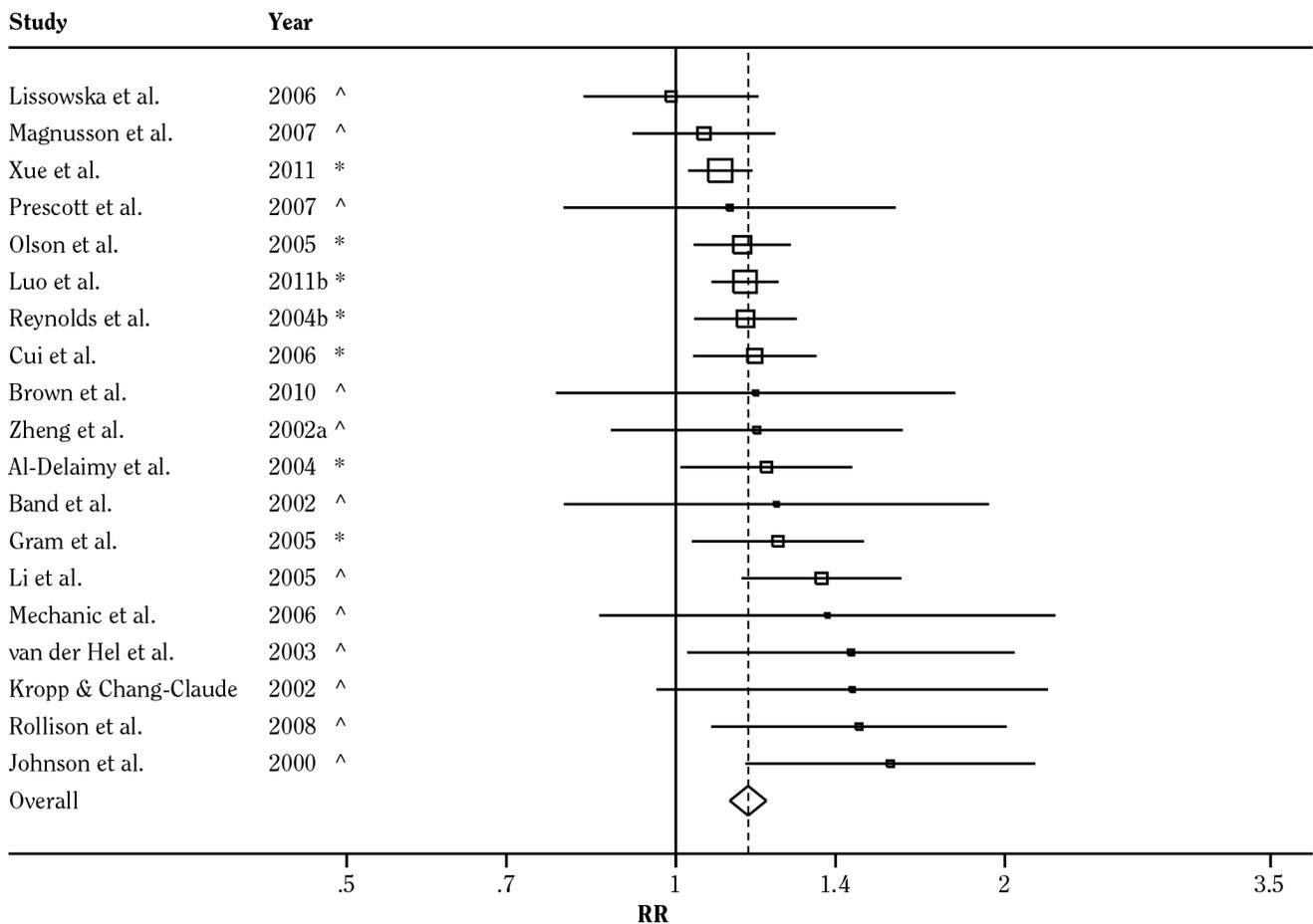
Cigarettes Smoked Per Day

The number of cigarettes smoked per day provides a measure of smoking intensity. In most studies, it represents the intensity of current smoking unless data are available for multiple time points that can be used to interpret the measure as the *usual* intensity of smoking, or intensity over time, the latter often expressed as pack-years of smoking. A recent study (Lubin et al. 2007) suggests that smoking intensity, measured as cigarettes per day, may have complex interactions with duration of smoking on risk of disease: high-intensity effects may diminish over time, while low-intensity effects increase. In contrast, associations of duration or pack-years of smoking with risk may involve residual confounding with age, as older women will have smoked longer but will also have increased risk for breast cancer regardless of smoking. While all studies included in the present meta-analyses of duration and pack-years of smoking adjusted for age, residual confounding may remain that could inflate estimates for longer duration or higher pack-years of smoking. Consequently, meta-analyses were conducted for studies that quantified risk of breast cancer with cigarettes per day, as well as duration of smoking and pack-years of smoking, to provide an alternative measure of dose-response.

A total of 20 studies (9 cohort, 11 case-control) provided a report on cigarettes per day as a measure of the intensity of smoking (Table 6.16SA and B) (Roddam et al. 2007) not included because only a continuous result was reported). Higher level of intensity was categorized at 20 cigarettes for 9 studies, at 21 for 6 studies, and at 25 for 3 studies. The cutpoint at 20 is consistent with smoking one pack of cigarettes or more per day. Two of the 20 eligible studies were excluded from the meta-analysis because in 1 (Gram et al. 2005) the highest category was 10 or more cigarettes per day and in the second (Lissowska et al. 2006) it was more than 14. Because the focus of the meta-analysis was on maximum dose, studies that have a maximum-dose category less than 20 have the potential to have subjects with substantially higher levels of smoking included with individuals who smoke considerably less.

Results for low-level compared with high-level smoking intensity differed on the order of 2.7% for all studies, 4.7% for cohort studies, and 3.4% for case-control studies.

Figure 6.35 Forest plot showing association between 20 or more years of smoking duration and risk for breast cancer, based on the subset of cohort studies before 2012 and case-control studies published from 2000 to 2011 (n = 19)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.16 (95% CI, 1.12–1.21); Begg $z = 1.57$, $p = 0.12$; Egger bias = 1.03, $p = 0.02$. See Table 6.17S (*note g*) for studies excluded. There were three studies with a cutpoint differing from 20 years by more than ± 2 years: 15 or more years (Zheng et al. 2002a and van der Hel et al. 2003) and 11 or more years (Magnusson et al. 2007). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

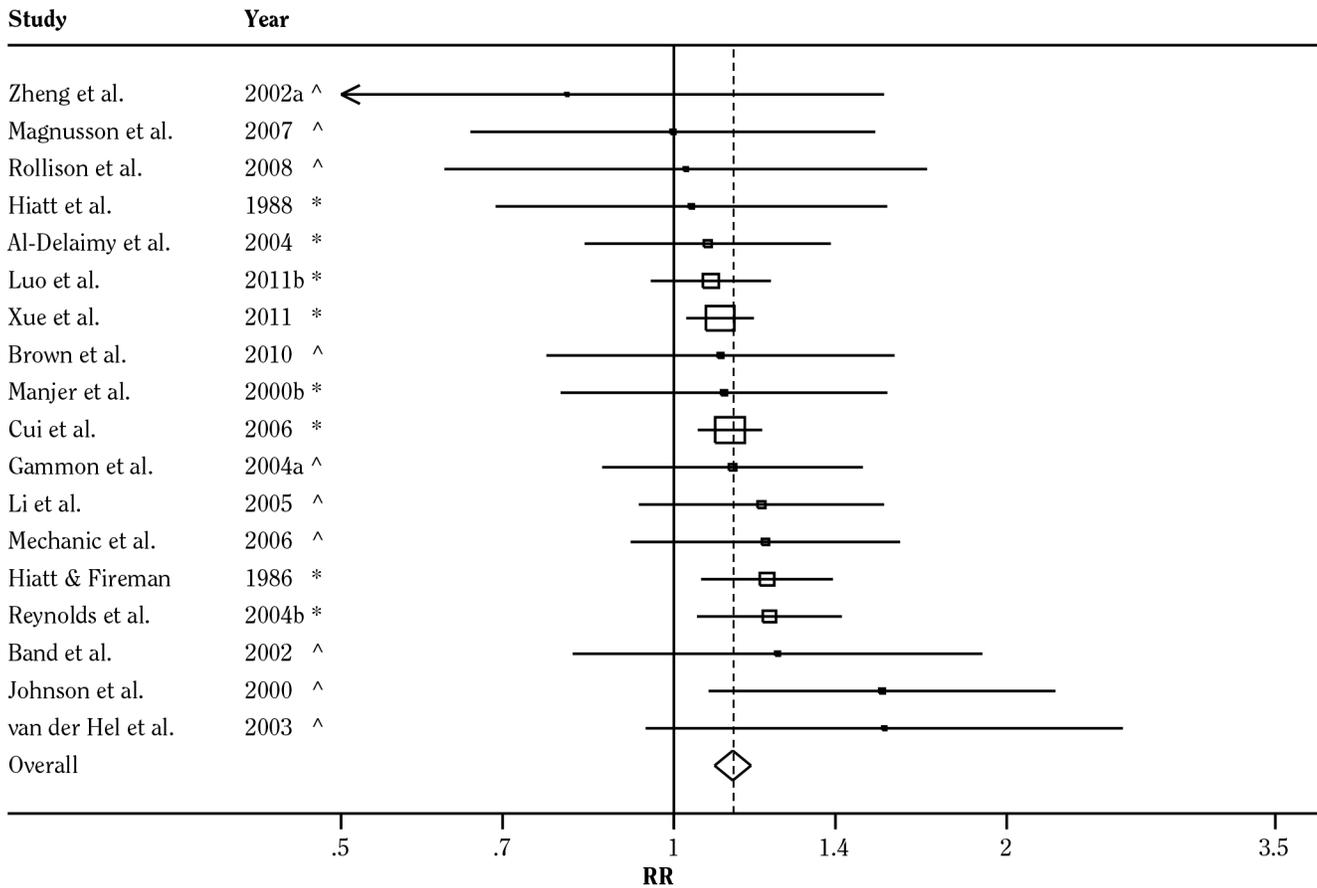
The summary estimate for the 18 studies was 1.10 (95% CI, 1.06–1.16; $p_h = 0.031$) for fewer than 20 cigarettes smoked per day. Although there was no evidence of publication bias according to the Begg’s statistic ($p = 0.103$), the Egger statistic ($p = 0.025$) suggested bias was present. The summary estimate was 1.13 (95% CI, 1.09–1.17; $p_h = 0.903$) for 20 or more cigarettes per day and there was no evidence of publication or small study bias according to Begg’s or Egger statistics (Table 6.17S, Figure 6.36). These results appear to be more heavily weighted by the 8 cohort studies. There was significant heterogeneity for

the 10 case-control studies for estimates involving 20 or fewer cigarettes per day ($p_h = 0.033$). When 3 case-control studies that used a no active/no passive reference group were excluded, the overall summary estimate was reduced to 1.08 (95% CI, 1.05–1.12, $p_h = 0.179$).

Pack-Years of Cigarette Smoking

The number of pack-years of smoking is calculated as the product of intensity (i.e., cigarettes smoked per day) and duration of smoking, and thus this indicator provides an index of lifetime dose of cigarette smoking.

Figure 6.36 Forest plot showing association between 20 or more cigarettes/day and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 18)

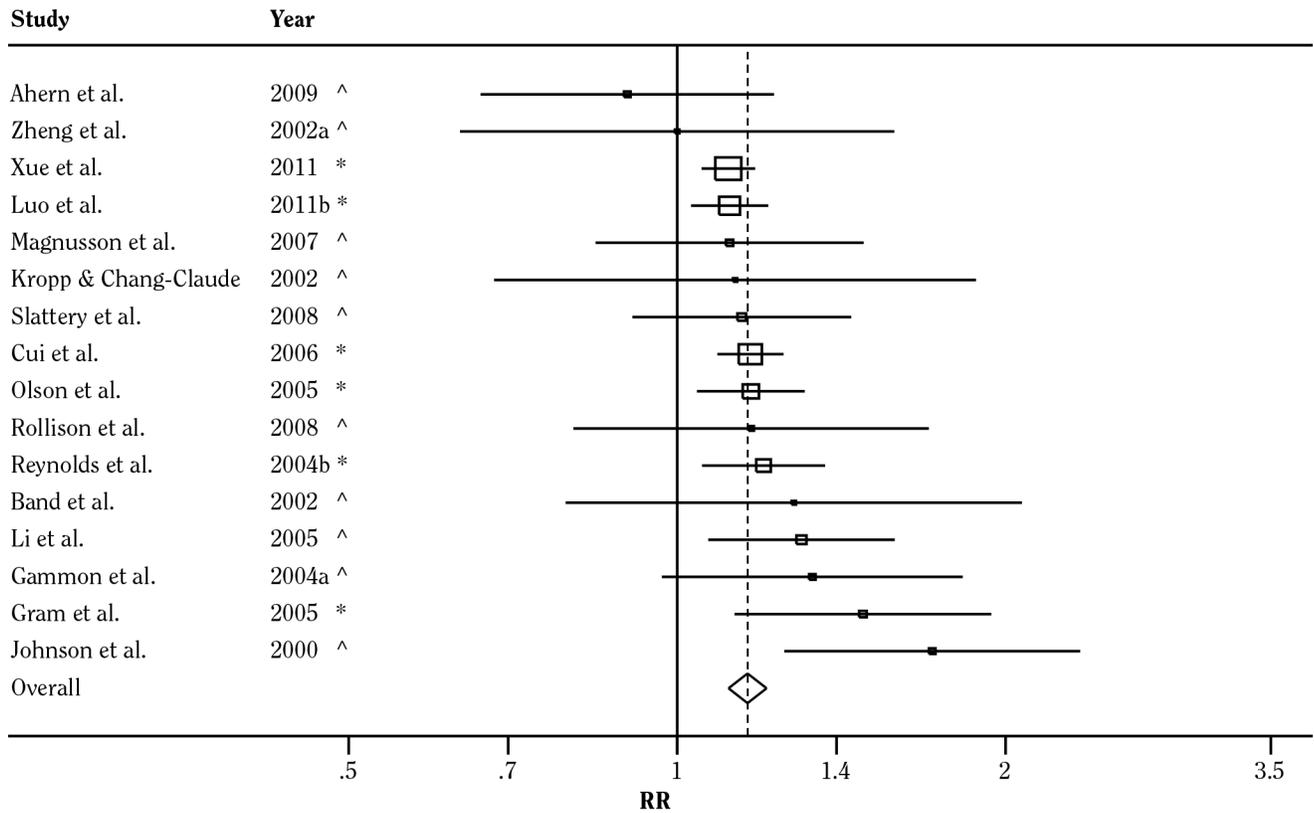


Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.13 (95% CI, 1.09–1.17); Begg $z = -0.34$, $p = 0.73$; Egger bias = 0.23, $p = 0.44$. See Table 6.17S (note h) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Some investigators prefer this measure, noting that it provides greater analytic power than duration alone (Ha et al. 2007). However, in their modeling of lung cancer and cigarette smoking, Lubin and Caporaso (2006) noted that the measure of pack-years mixes low-intensity smoking over long durations with high-intensity smoking over short periods. Low-dose smoking over a long duration results in increasing trends for risk estimates, termed *exposure enhancement*, and high-dose smoking over short periods produces the reverse trend, termed *reduced potency* (Lubin and Caporaso 2006). In addition, estimates of the usual number of cigarettes smoked per day lose validity over longer durations if smoking is punctuated by intermittent attempts at cessation.

Sixteen studies (6 cohort and 10 case-control) have examined the association between risk for breast cancer and pack-years of smoking and were included in the meta-analysis (Table 6.16SA and B). The summary estimate (RR) for the 16 studies was 1.16 (95% CI, 1.11–1.21; $p_h = 0.304$) for 20 or more pack-years of smoking (Table 6.17S, Figure 6.37). The Begg and Egger tests did not reveal any bias (see notes for Figure 6.37). Estimates for 20 or more pack-years did not differ meaningfully between study types: cohort (RR = 1.15; 95% CI, 1.10–1.19; $p_h = 0.346$) and case-control (RR = 1.21; 95% CI, 1.09–1.34; $p_h = 0.314$) (Table 6.17S). After excluding 1 cohort (Gram et al. 2005) and 3 case-control studies with estimates based on only

Figure 6.37 Forest plot showing association between 20 or more pack-years of smoking and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 16)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.16 (95% CI, 1.11–1.21); Begg z = 0.54, p = 0.59; Egger bias = 0.56, p = 0.23. See Table 6.17S (note i) for studies excluded. There was one study with a cutpoint differing from 20 pack-years by more than ± 5 years: 28 or more years (Li et al. 2005). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

a no active/no passive exposure reference group (Johnson et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004a), the overall summary estimate for 20 or more pack-years was slightly attenuated (RR = 1.14; 95% CI, 1.10–1.18; $p_h = 0.829$), and the RR for case-control studies was reduced by 6%. The overall summary estimate was 1.14 (95% CI, 1.10–1.18; $p_h = 0.900$) with the exclusion of the case-control study by Li and colleagues (2005), which had a higher cutpoint (more than 52 pack-years) and included only postmenopausal women. The exclusion of this study sharply reduced the RR for the case-control studies to 1.09 (95% CI, 0.96–1.24; $p_h = 0.795$).

The summary estimate for less than 20 pack-years of smoking was 1.09 (95% CI, 1.03–1.15; $p_h = 0.099$), which was below the summary estimate of 1.16 (95% CI,

1.11–1.21) for 20 or more pack-years (Table 6.17S). This result was primarily due to the cohort studies, for which the summary estimate for fewer than 20 pack-years was 1.04 (95% CI, 1.00–1.09; $p_h = 0.872$). The result for fewer than 20 pack-years of smoking for case-control studies was substantially higher (RR = 1.20; 95% CI, 1.05–1.37) but the heterogeneity was significant ($p_h = 0.023$). The summary estimate and the extent of heterogeneity for these case-control studies were substantially decreased when the three studies (Johnson et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004a) using a no active/no passive exposure reference group were excluded (RR = 1.10; 95% CI, 0.97–1.24; $p_h = 0.154$). Overall, accumulating 20 or more pack-years increased risk for breast cancer by a significant average of 16%, while smoking

for less than 20 pack-years was associated with a smaller increased risk of 9%. The estimate for 20 or more pack-years of smoking may be conservative, because some studies indicate that risk continues to rise with more pack-years (Xue et al. 2011).

Thirteen of the 16 studies with estimates for pack-years of smoking also provided risk by duration (Table 6.16S). Estimates across levels of duration and pack-years of smoking were not necessarily consistent for the two measures within a study; the Spearman correlation across studies was 0.62 ($p = 0.02$). Nonetheless, the summary estimates suggest that long duration of smoking and higher numbers of pack-years of smoking significantly increase risk for breast cancer by a similar amount, approximately 11–21% based on the CIs, depending on study design and sensitivity analysis restrictions (Table 6.17S). The summary estimate from case-control studies tended to be higher for both duration and pack-years of smoking than for cohort studies but also less stable. Taken together, the meta-analyses for duration, cigarettes smoked per day, and pack-years provide similar evidence for a dose-response relationship between smoking and breast cancer.

Timing of Exposure to Tobacco Smoke

The timing of smoking relative to critical periods of change in the size and morphology of breast tissue—time-frames such as menarche, during adolescence, or before first pregnancy—may be important. Based on *in vitro* studies, Russo (2002) hypothesized that smoking is more likely to induce neoplastic changes during these periods, when the susceptibility of the breast to carcinogens is increased. Breast cancer also is more likely to develop in undifferentiated tissues that may be susceptible to tobacco-related and other carcinogens. Results of epidemiologic studies substantiate that nulliparous women have a higher risk than parous women of breast cancer. The lower risk for parous women is attributed to having an early full-term pregnancy and the subsequent increased differentiation in the terminal ducts of the breast (Russo et al. 1992, 2000; Russo and Russo 1995, 2008).

Age at Smoking Initiation

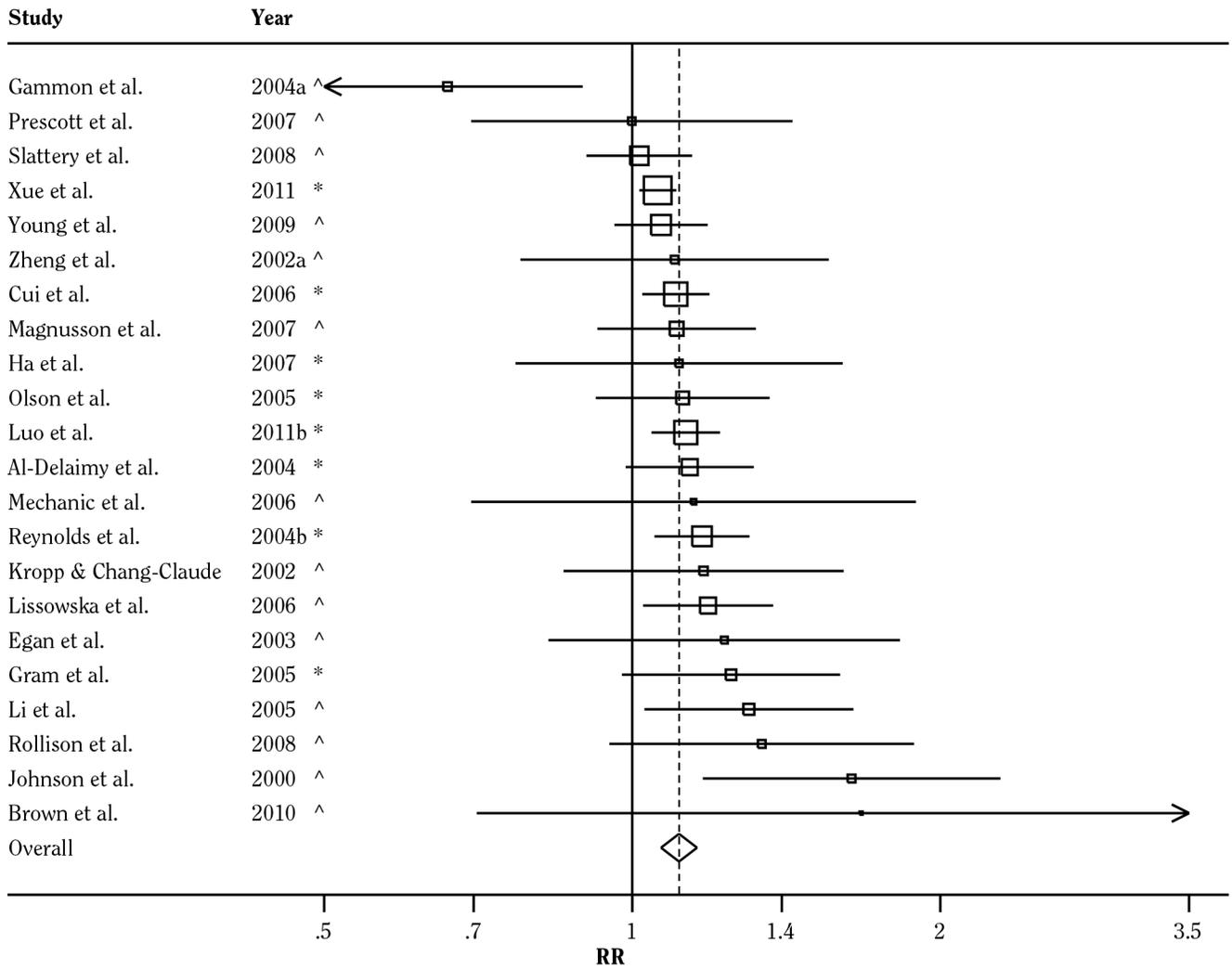
Twenty-two studies with data for age at smoking initiation were evaluated: 8 cohort studies and 14 case-control studies (Table 6.16S, see notes for Figure 6.38 for exclusions). The cutpoints for age varied among these studies. Therefore, estimates were allocated into the closest of the following categories: younger than 16 years of age, 16–19 years of age, and 20 years of age and older. The

first two categories were combined so that all 22 studies had estimates for those younger than 20 years of age at smoking initiation. Sensitivity analyses stratified the studies by design and excluded studies with large differences in cutpoints or those that used only a no active/no passive exposure reference group.

Figure 6.38 shows results from all 22 studies for those younger than 20 years of age at smoking initiation. The RR summary estimate was 1.11 (95% CI, 1.07–1.16; $p_h = 0.088$) (Table 6.17S). The Begg and Egger tests were not significant (see notes to Figure 6.38; funnel plot not shown). The estimate for the 8 cohort studies (RR = 1.09; 95% CI, 1.06–1.13; $p_h = 0.541$) was similar to that for the 14 case-control studies (RR = 1.12; 95% CI, 1.02–1.22; $p_h = 0.029$) (Table 6.17S). One cohort study (Gram et al. 2005) and 5 case-control studies (Johnson et al. 2000; Kropp and Chang-Claude 2002; Gammon et al. 2004a; Mechanic et al. 2006; Young et al. 2009) were excluded from the analysis because estimates were based on a no active/no passive exposure reference group. One study was excluded because the age cutpoint was 16 years of age or younger (Egan et al. 2003). These exclusions did not meaningfully alter the summary estimate (RR = 1.09; 95% CI, 1.06–1.13; $p_h = 0.597$). Nineteen studies (7 cohort, 12 case-control) estimated risk when smoking was initiated at 16 or fewer years of age (RR = 1.08; 95% CI, 1.00–1.15; $p_h = 0.065$).

Only 13 studies (6 cohort, 7 case-control) reported estimates of risk when smoking initiation occurred from 16–19 years of age (RR = 1.11; 95% CI, 1.07–1.15; $p_h = 0.757$). Additionally, results for the meta-analysis of the 19 studies that reported estimates for smoking initiation at 20 years of age and older showed a significant summary estimate (RR = 1.08; 95% CI, 1.05–1.12; $p_h = 0.672$) (Table 6.17S). This estimate was only slightly lower than that for those younger than 20 years of age. Thus, these studies did not reveal a clear trend for a change in summary estimates across categories for age at initiation. Few studies tested for trends across age categories and estimates for most studies included in the meta-analyses were similar for those 16 years of age and younger and those 20 years of age or younger (Spearman rank-order correlation = 0.81, $p < 0.0001$). Of note, the estimates in the tails of the distribution of the RRs across studies with either significant protective or increased estimates are from studies that used a no active/no passive exposure reference group. Taken together, the meta-analyses of these studies did not provide clear evidence that initiating smoking during adolescence or young adulthood confers any greater risk than initiation at older ages.

Figure 6.38 Forest plot showing association between less than 20 years of age at smoking initiation and risk for breast cancer, based on the subset of cohort studies published before 2012 and case-control studies published from 2000 to 2011 (n = 22)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.11 (95% CI, 1.07–1.16); Begg z = 0.59, p = 0.55; Egger bias = 0.63, p = 0.12. See Table 6.17S (note j) for studies excluded. There were six studies with a cutpoint differing from 20 years of age at smoking initiation by more than ± 2 years: 15 years of age and younger (Prescott et al. 2007), 16 years of age and younger (Egan et al. 2003), and 18 years of age and younger (Gammon et al. 2004a; Mechanic et al. 2006; Olson et al. 2005; Rollison et al. 2008). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. CI = confidence interval; RR = relative risk.

Smoking Before or During First Full-Term Pregnancy

The effects of smoking before versus after a first full-term pregnancy may be confounded by effects associated with early age at smoking initiation and age at first pregnancy (Cui et al. 2006). Few studies have examined the risk of smoking during pregnancy, for which the results may differ for women who stop smoking when pregnant than for those who continue to smoke during pregnancy. Lawlor and colleagues (2004) conducted a meta-analysis of 11 studies, 2 of which were based on smoking during pregnancy (Innes and Byers 2001; Fink and Lash 2003), to assess the effect of smoking before a first full-term pregnancy. The analysis included estimates from their own cohort, the British Women's Heart and Health Study, 2 earlier cohort studies (Egan et al. 2002; Reynolds et al. 2004b), and 8 case-control studies (Adami et al. 1988; Hunter et al. 1997; Lash and Aschengrau 1999, 2002; Innes and Byers 2001; Band et al. 2002; Kropp and Chang-Claude 2002; Fink and Lash 2003). Based on 6,528 cases, the RR summary estimate was 1.07 (95% CI, 0.94–1.22). The risk was attenuated when 2 influential studies with wide CIs (Lash and Aschengrau 1999; Innes and Byers 2001) were removed (RR = 1.03; 95% CI, 0.93–1.14), which also reduced heterogeneity. These 2 studies and an earlier one based on the NHS-I (Hunter et al. 1997) were 3 of the 11 that reported statistically significant results.

DeRoo and colleagues (2011b) published a meta-analysis on a larger number of studies than the earlier review by Lawlor and colleagues (2004). These authors included an additional 15 reports (Morabia et al. 1996; Egan et al. 2003; Al-Delaimy et al. 2004; Gammon et al. 2004a; Gram et al. 2005; Li et al. 2005; Olson et al. 2005; Cui et al. 2006; Lissowska et al. 2006; Ha et al. 2007; Magnusson et al. 2007; Prescott et al. 2007; Rollison et al. 2008; Slattery et al. 2008; Young et al. 2009). They excluded 2 studies of smoking during first pregnancy based on linked birth and cancer registry data (Innes and Byers 2001; Fink and Lash 2003) and 1 study (Hunter et al. 1997) that overlapped with a subsequent report (Egan et al. 2002); these 3 (i.e., all but Egan et al. 2002) were included in Lawlor and colleagues' (2004) meta-analysis. DeRoo and colleagues' (2011b) summary estimate was 1.11 (95% CI, 1.06–1.16). This higher estimate than that of Lawlor and colleagues (2004) was influenced by several large cohort and case-control studies published between January 2004 and 2009.

Twenty-two studies included in this report provided RR estimates for smoking before or during first full-term pregnancy for the meta-analysis: 9 cohort studies (Al-Delaimy et al. 2004; Lawlor et al. 2004; Reynolds et al. 2004b; Gram et al. 2005; Olson et al. 2005; Cui et al. 2006; Ha et al. 2007; Luo et al. 2011b; Xue et al. 2011) and

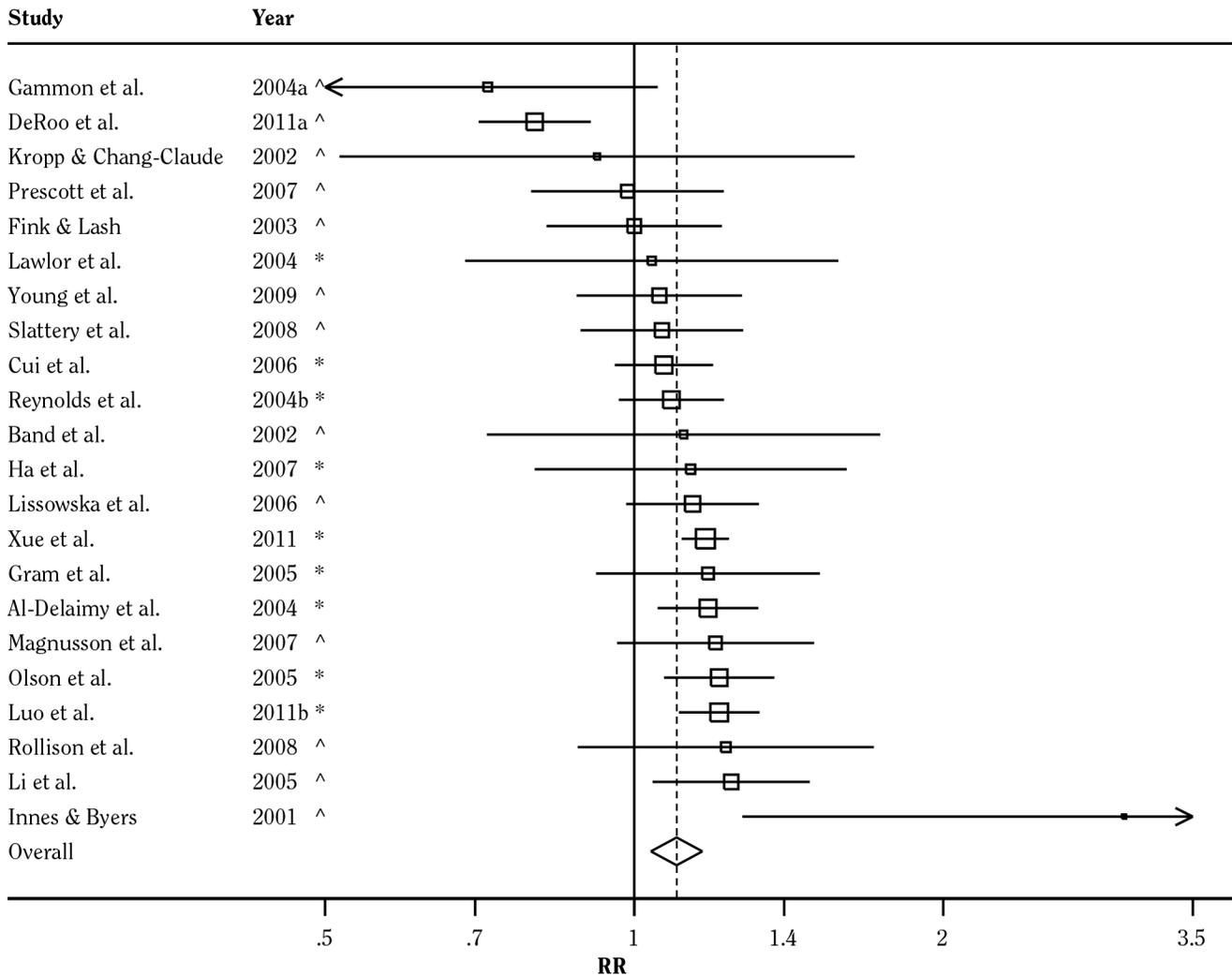
13 case-control studies (Innes and Byers 2001; Band et al. 2002; Kropp and Chang-Claude 2002; Fink and Lash 2003; Gammon et al. 2004a; Li et al. 2005; Lissowska et al. 2006; Magnusson et al. 2007; Prescott et al. 2007; Rollison et al. 2008; Slattery et al. 2008; Young et al. 2009; DeRoo et al. 2011a) (Table 6.16S, see notes for Figure 6.39 for exclusions). For these 22 studies, the RR summary estimate was 1.10 (95% CI, 1.04–1.17; $p_h = <0.001$) (Table 6.17S). This summary result is higher and statistically significant compared with that of Lawlor and colleagues (2004), primarily because it included 5 recent, large cohort studies that reported significant estimates (Al-Delaimy et al. 2004; Gram et al. 2005; Olson et al. 2005; Luo et al. 2011b; Xue et al. 2011). The RR summary estimate was 1.16 (95% CI, 1.12–1.20; $p_h = 0.746$) for the 9 cohort studies and 1.05 (95% CI, 0.94–1.18; $p_h = 0.001$) for the 13 case-control studies (Table 6.17S). After excluding 1 cohort study (Gram et al. 2005) and 3 case-control studies (Gammon et al. 2004a; Kropp and Chang-Claude 2002; Young et al. 2009) that were based on estimates using only a no active/no passive exposure reference group, the overall summary estimate increased slightly (RR = 1.11; 95% CI, 1.05–1.18; $p_h \leq 0.001$) due to the increase for case-control studies (RR = 1.09; 95% CI, 0.96–1.23; $p_h \leq 0.001$). The additional exclusion of the 3 case-control studies, which reported estimates for smoking only during pregnancy (Innes and Byers 2001; Fink and Lash 2003; DeRoo et al. 2011a), further increased the RR for case-control studies to 1.13 (95% CI, 1.05–1.23), eliminating the significant heterogeneity ($p_h = 0.727$). In addition, the overall summary estimate was increased to 1.16 (95% CI, 1.12–1.20; $p_h = 0.830$). Thus, the 3 case-control studies with risk estimates for smoking only during pregnancy produced heterogeneity and attenuated summary estimates, but those that used a no active/no passive exposure reference group had little or no effect on the summary estimates.

These summary estimates for smoking before or during first pregnancy are only slightly higher than those for ever smoking, and they are quite similar to those for duration of 20 or more years and 20 or more pack-years of smoking. Overall, the studies conducted since 2000 do not provide clear evidence that smoking before first pregnancy confers a greater risk than smoking at any other time in a woman's life. Taken together, the results for earlier age at smoking initiation and smoking before first pregnancy do not support the hypothesis that smoking has greater carcinogenic effects during periods in which breast tissue is less differentiated and theoretically more susceptible.

Menopausal Status

Risk for breast cancer is associated with duration and level of estrogen exposure and evidence suggests that

Figure 6.39 Forest plot showing association between smoking before or during first full-term pregnancy and risk for breast cancer, based on the subset of cohort studies before 2012 and case-control studies published from 2000 to 2011 (n = 22)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.10 (95% CI, 1.04–1.17); Begg z = -1.16, p = 0.25; Egger bias = -0.50, p = 0.43. See Table 6.17S (note m) for studies excluded. Estimates based on exposure before first pregnancy with the exception of three studies, which reported an estimate based on exposure during first pregnancy (Innes and Byers 2001; Fink and Lash 2003; DeRoo et al. 2011a). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. CI = confidence interval; RR = relative risk.

the phenotypic heterogeneity of breast cancer is linked to menopausal status (Lipton 2005). Spicer and Pike (2005) hypothesized that because menopause is associated with a decreased rate of breast cell proliferation compared with that in the premenopausal period, it modifies susceptibility to exposures such as obesity, hormone therapy, and alcohol. It is plausible that if smoking affects hormone

metabolism, the risk of breast cancer due to smoking is similarly modified by menopause.

For some risk factors, such as obesity, risk estimates differ when analyses are stratified by menopausal status (van den Brandt et al. 2000). Menopause could modify the risk of breast cancer associated with smoking by altering hormone metabolism and the sensitivity of breast tissue

to tobacco carcinogens (Kendall et al. 2007). Women who smoke—primarily current, heavy smokers—experience menopause at an earlier age than those who do not smoke (Baron et al. 1990; Midgette and Baron 1990; Kato et al. 1998; Mikkelsen et al. 2007; Sun et al. 2012) and have a higher risk for osteoporosis even when on estrogen therapy (North American Menopause Society 2010), which may be due to altered estrogen metabolism and lower estrogen levels (Kiel et al. 1992). These observations support an anti-estrogenic effect of smoking (Kendall et al. 2007). However, smokers also tend to be leaner, drink more alcohol, and have poorer diets than nonsmokers; all of these factors are also associated with early menopause (Sampson 2002). Moreover, results from several studies have not provided sufficient evidence that estradiol levels in current smokers differ from those in former or never smokers (Longcope and Johnston 1988; Baron et al. 1990; Key et al. 1991; Cassidenti et al. 1992; Kendall et al. 2007; Arslan et al. 2009). Even so, in a recent cross-sectional analysis of the association between endogenous hormones and several risk factors for breast cancer, the levels of all sex hormones were reported to be higher for women who smoked 15 or more cigarettes per day than for never smokers. Hormonal levels, particularly for estrogen, were attenuated with adjustment for BMI, whereas further adjustment for alcohol did not result in any meaningful change (Endogenous Hormones and Breast Cancer Collaborative Group 2011).

Previous reviews did not find evidence to suggest that menopause modifies the risk of breast cancer from smoking (Egan et al. 2002; Terry and Rohan 2002). The Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002) reported an RR of 1.07 (standard error = 0.05) for premenopausal women and an RR of 1.12 (standard error = 0.06) for women 50 years of age and older who experienced natural menopause.

Several studies have examined menopausal status specifically, and several have conducted formal tests for interaction with smoking. Table 6.18S shows results for ever smoking from 14 studies stratified by menopausal status and 6 studies in which the entire study sample included only one menopausal group. Of the 20 studies listed, 7 reported data for pack-years of smoking for both menopausal groups and 3 reported results for postmenopausal women only. Overall, results for ever smoking were highly variable for both premenopausal and postmenopausal risks. Menopause can be difficult to define in observational studies, however, which can result in misclassification bias, particularly when age is the only criterion for menopause. Furthermore, not all studies in Table 6.18S accounted for residual confounding by hormonal status or use of HRT. A sensitivity analysis (Table 6.18S)

provides the RR for case-control studies, with the study by Kruk (2007) excluded because of its extreme estimates.

Menopausal Status—Ever Smoking

Among 17 studies, 3 cohort (Hiatt and Fireman 1986; Manjer et al. 2000b; Xue et al. 2011) and 3 case-control (Band et al. 2002; Lissowska et al. 2006; Kruk 2007) studies reported a significantly increased risk for premenopausal women associated with ever smoking. All but 6 studies had an RR greater than 1.10, and no significant inverse associations were reported. The summary estimate (RR) associated with premenopausal smoking for all studies combined was 1.26 (95% CI, 1.11–1.43; $p_h \leq 0.001$) (Table 6.18S). This RR was reduced to 1.18 (95% CI, 1.08–1.29; $p_h = 0.005$) when the single outlying estimate for a case-control study (RR = 2.34) (Kruk 2007) was excluded (Table 6.18S). The summary estimate for the case-control studies was reduced from 1.30 (95% CI, 1.04–1.62; $p_h = 0.001$) to 1.20 (95% CI, 1.02–1.42; $p_h = 0.075$) when the outlier was excluded, a value that is quite similar to the RR for the 4 cohort studies (RR = 1.16; 95% CI, 1.08–1.24; $p_h = 0.628$) (Table 6.18S).

A total of 17 studies reported results for smoking by postmenopausal women. Four out of 6 cohort studies reported positive associations of 1.10 or greater, of which 2 were significant (Olson et al. 2005; Luo et al. 2011b). One cohort study (Xue et al. 2011), however, reported a significant inverse association (RR = 0.91; 95% CI, 0.86–0.96). Three of the 11 case-control studies that included postmenopausal women reported significant positive associations for this group (Johnson et al. 2000; Li et al. 2005; Kruk 2007). Five studies reported an RR greater than 1.10, and none reported a significant inverse association. The summary estimate associated with postmenopausal women for all studies combined was 1.10 (95% CI, 1.02–1.19; $p_h = 0.001$) (Table 6.18S). This RR was reduced to 1.07 (95% CI, 1.00–1.14; $p_h = 0.001$) when the outlying estimate (RR = 1.76) (Kruk 2007) was removed. The summary estimate for the case-control studies was reduced from 1.13 (95% CI, 1.01–1.27; $p_h = 0.001$) to 1.07 (95% CI, 0.98–1.16; $p_h = 0.147$) when the outlier was removed, an estimate virtually identical to the estimate based on the 6 cohort studies (RR = 1.07; 95% CI, 0.97–1.19; $p_h = 0.001$) (Table 6.18S).

Several issues should be considered when evaluating these results for ever smoking in premenopausal versus postmenopausal women. First, the estimates reported by Kruk (2007) are outliers for both menopausal groups and, when these estimates are included, the summary estimates (RRs) are positively biased. The significant inverse association in postmenopausal women reported

by Xue and colleagues (2011) for the NHS-I contrasts with the significant positive associations reported by two other large cohort studies, Women's Health Initiative (Luo et al. 2011b) and the Iowa Women's Health Study (Olson et al. 2005). Previous reports from NHS-I (London et al. 1989; Egan et al. 2002) have indicated a null association and no meaningful difference between menopausal groups, but they were based on fewer cases and less follow-up time than the recent report by Xue and colleagues (2011).

Among the case-control studies, the study by Johnson and colleagues (2000) also provided estimates for smoking by menopausal status that used a small no active/no passive exposure reference group: for premenopausal women, OR = 2.3 (95% CI, 1.2–4.5), and for postmenopausal women, OR = 1.5 (95% CI, 1.0–2.3). These estimates contrast strongly with their results when using a no active-only reference group (Table 6.18S): premenopausal women (OR = 1.0; 95% CI, 0.80–1.3); postmenopausal women (OR = 1.2; 95% CI, 1.0–1.4). No other study has contrasted estimates using these two reference groups by menopausal status. It is important to note that Johnson and colleagues (2000) restricted their analysis using a no active/no passive exposure reference group to the approximate 60% of women who reported their residential exposure to passive smoke for at least 90% of their lifetime. This makes a direct comparison of their results difficult.

Menopausal Status—Pack-Years of Smoking

Several studies have reported results for pack-years by menopausal status: 7 for premenopausal and 10 for postmenopausal (Table 6.18S). The results across these studies are variable and inconsistent. Two cohort studies that reported results for premenopausal women (Reynolds et al. 2004b; Xue et al. 2011) found significantly increased risks for the highest category of pack-years of smoking (≥ 30) (RR = 2.05; 95% CI, 1.20–3.49 and RR = 1.27; 95% CI, 1.16–1.38, respectively). Among 5 case-control studies offering estimates for premenopausal women, 2 reported statistically significant positive associations for the highest level of pack-years of smoking (Band et al. 2002: RR = 1.69; 95% CI, 1.10–2.61 for ≥ 20 pack-years; Slattery et al. 2008: RR = 1.6; 95% CI, 1.1–2.4 for >15 pack-years) in non-Hispanic Whites, while 1 (Johnson et al. 2000) found significant increased risks for fewer pack-years of exposure (RR = 2.30; 95% CI, 1.10–4.70 for 11–20, and RR = 2.40; 95% CI, 1.20–4.70 for 1–10 pack-years). The other 2 studies (Zheng et al. 2002a; Ahern et al. 2009) were essentially null for the association between breast cancer and pack-years of smoking in premenopausal women.

Four cohort and six case-control studies reported estimates for the association of pack-years of smoking

with breast cancer in postmenopausal women. The pooled estimate for 20 or more pack-years was statistically significant in Reynolds and colleagues (2004b) (pooled RR = 1.17; 95% CI, 1.01–1.35), Olson and colleagues (2005) (pooled RR = 1.17; 95% CI, 1.04–1.31), and Luo and colleagues (2011b) (pooled RR = 1.12; 95% CI, 1.03–1.21). Luo and colleagues (2011b) also found a statistically significant increased risk for smoking more than 50 pack-years (RR = 1.18; 95% CI, 1.02–1.22). In contrast, there was a trend toward lower risk with more pack-years of smoking in Xue and colleagues (2011), which reached statistical significance for the highest level of more than 15 pack-years (RR = 0.88; 95% CI, 0.79–0.99). In contrast, only two (Johnson et al. 2000; Li et al. 2005) of the six case-control studies reported statistically significant associations for the highest level of pack-years of smoking in postmenopausal women (RR = 1.60; 95% CI, 1.00–2.60, and RR = 1.30; 95% CI, 1.00–2.60, respectively). It should be noted that the estimates reported by Johnson and colleagues (2000) were based on a no active/no passive exposure reference group.

Only one cohort study (Reynolds et al. 2004b) formally tested for interaction between menopause and smoking across multiple measures. This study found no significant results by the likelihood ratio test for duration of smoking ($p = 0.80$); cigarettes/per day ($p = 0.42$); pack-years of smoking ($p = 0.07$); and years since cessation ($p = 0.76$).

Menopausal Status—Summary

The results in Table 6.18S indicate that considerable heterogeneity exists among studies that report estimates for the association of smoking with breast cancer by menopausal status, although none of the summary estimates was associated with statistically significant publication bias. Although the results of the meta-analysis suggest that risk is greater in premenopausal than in postmenopausal women, it remains uncertain whether the association of smoking with breast cancer differs by menopausal status.

Hormone Receptor Status

ERs and progesterone receptors (PRs) mediate the effects of estrogen and progesterone on the growth, proliferation, and differentiation of breast tumors; response to hormonal treatment; recurrence; and survival. Palmer and Rosenberg (1993) postulated that the expression status of ERs could modulate the anti-estrogenic effects of smoking, and Meek and Finch (1999) reported that smoking alters the expression of ERs. The presence (+) or absence (–) of ER expression in breast tumors is increasingly

recognized as a potential biomarker of etiologically distinct subtypes (Anders et al. 2008; Bertucci et al. 2009; Onitilo et al. 2009). Consequently, some of the more recent studies stratify analyses on ER expression. The information added by cross-classification with the status of PRs remains controversial. In addition to reporting the expression status of ERs and PRs, studies have begun to cross-classify cases by the status of human epidermal growth factor receptor 2 (HER2) because the so-called *triple negative* phenotype (i.e., the combination of negative ER, PR, and HER2 status) is increasingly recognized as distinct and having a poor prognosis (Bauer et al. 2007; ReisFilho and Tutt 2008; Gluz et al. 2009).

Many studies have assessed the risk of breast cancer based on the status of ER expression. In 2 early, small hospital-based studies, Daniell (1980) and Ranocchia and colleagues (1991) observed that the prevalence of smoking was higher among breast cancer cases with ER- tumors than in cases with ER+ tumors, but these studies were underpowered and the data were not rigorously analyzed. Table 6.19S summarizes data from 17 studies that assessed whether the risk for breast cancer differs by ER expression status for ever smoking or by the highest category of cigarettes smoked per day. Althuis and colleagues (2004) reviewed 10 of the studies shown in Table 6.19S (McTiernan et al. 1986; Stanford et al. 1987; Cooper et al. 1989; London et al. 1989; Yoo et al. 1997; Morabia et al. 1998; Huang et al. 2000a; Manjer et al. 2001; Britton et al. 2002; Cotterchio et al. 2003) with hormone receptor-defined breast cancer and found no evidence for a differential association between breast cancer and smoking by hormonal phenotype, but they did not provide a numerical analysis. Four of these studies (Cooper et al. 1989; London et al. 1989; Yoo et al. 1997; Morabia et al. 1998) were reviewed in the 2006 Surgeon General's report.

Hormone Receptor Status—Ever Smoking

Findings from the 17 studies on the association of ever smoking with breast cancer defined by ER status are highly inconsistent (Table 6.19S). Four studies reported significantly increased risks for ER+ breast cancer with ever smoking, with RRs ranging from 1.15–1.42 (Yoo et al. 1997; Al-Delaimy et al. 2004; Li et al. 2005; Luo et al. 2011b). Two studies reported significantly increased risks for ER–breast cancer (Cooper et al. 1989; Manjer et al. 2001), with RRs ranging from 1.63–2.41. One study (Morabia et al. 1998) reported significantly increased risks for both ER+ and ER– breast cancer, with a somewhat stronger association with ER– (RR = 4.01; 95% CI, 1.90–8.46) than ER+ (RR = 2.28; 95% CI, 1.56–3.35) tumors. This study is the only one that used a no active/no passive exposure reference group (Morabia et al. 1998).

The recent case-control study by Rabstein and colleagues (2010) found a significant inverse association with ER+ breast cancer (RR = 0.79; 95% CI, 0.65–0.95), but no association with ER– breast cancer. The remaining studies reported null results (McTiernan et al. 1986; Stanford et al. 1987; London et al. 1989; Huang et al. 2000a; Britton et al. 2002; Cotterchio et al. 2003; Gammon et al. 2004a; Lissowska et al. 2006; Trivers et al. 2009).

Hormone Receptor Status—Cigarettes Smoked Per Day

Only six studies have reported results on the association between cigarettes smoked per day and breast cancer defined by ER status, and these are also very inconsistent (Table 6.19S). One study (London et al. 1989) reported a significantly increased risk for ER+ breast cancer with 25 or more cigarettes smoked per day (RR = 1.38; 95% CI, 1.04–1.84), and another (Al-Delaimy et al. 2004) reported significantly increased risks for ER+ breast cancer with fewer cigarettes smoked per day: RR = 1.46; 95% CI, 1.14–1.87 for 5–14 cigarettes smoked per day; and RR = 1.45; 95% CI, 1.09–1.93 for 1–4 cigarettes smoked per day. Manjer and colleagues (2001) found significantly increased risks for ER– breast cancer regardless of number of cigarettes smoked per day, and Morabia and colleagues (1998) reported significantly increased risks for both ER+ and ER– breast cancer regardless of level, although the association was somewhat stronger in women with ER– tumors. The remaining two studies reported essentially null results (Li et al. 2005; Lissowska et al. 2006).

Hormone Receptor Status—Methodologic Issues

Some issues affect the interpretation of published results for smoking and breast cancer by hormone receptor status. First, all but two studies (London et al. 1989; Al-Delaimy et al. 2004) in Table 6.19S used case-control designs, which are more subject to bias than other study designs. Second, methods for detecting ER expression have changed over time, and some older studies were based on a mix of methods (Ross and Hortobagyi 2005). Many studies rely on incomplete or inaccurate pathology and medical records and ER status is generally not obtained on in situ tumors. The completeness of data for ER status in the studies in Table 6.19S ranged from 40–100%. Third, few studies have identified consistent risk factors for the ER– phenotype other than race and younger age (Althuis et al. 2004), and thus potential confounders for this type of breast cancer are not yet well characterized. Last, researchers are not sure whether ER status should be cross-classified with PR status. The most recent studies

have characterized breast cancer phenotypes by the combination of ER, PR, and HER2 status or by gene expression phenotypes (luminal A, B, basal-like) (Kwan et al. 2009; Trivers et al. 2009). Kabat and colleagues (2011) recently published an analysis from the Women's Health Initiative on risk of the triple negative phenotype compared with risk for ER+ breast cancer in relation to smoking. RRs (not shown in Table 6.19S) were significantly increased in women with ER+ breast cancer for former smoking (1.14; 95% CI, 1.05–1.24), duration of 30 or more years (1.14; 95% CI, 1.01–1.28), 40 or more pack-years of smoking (1.25; 95% CI, 1.06–1.44), and younger than 20 years of age at initiation (1.16; 95% CI, 1.05–1.28). In contrast, there were no significant associations in women with triple negative breast cancer. These results are quite similar to those reported by Luo and colleagues (2011b), who also analyzed tumors by ER/PR status only (not HER2) data from the Women's Health Initiative cohort.

Hormone Receptor Status—Summary

In summary, results from studies conducted to date are inconsistent on the association of smoking with different phenotypes of breast cancer defined on the basis of hormone receptor status.

Exposure to Tobacco Smoke and Risk of Second Primary Contralateral Breast Cancer

Although a recent study indicates that there was a downward trend in the incidence of contralateral breast cancer in the United States from 1975–2006 (Nichols et al. 2011), a summative review published in 1999 documented prevalence estimates ranging from 2–11% (Chen et al. 1999), and a follow-up of 305,533 breast cancer cases in the SEER Program database provided an estimate of 4.3% for the development of a second primary contralateral breast cancer (Bernstein et al. 2003).

A second primary breast cancer has most frequently been defined as a new and independent tumor, although studies have varied on whether carcinoma in situ has been included. The risk of developing a second primary contralateral breast cancer has been evaluated in a number of studies (Kato et al. 1986; Horn and Thompson 1988; Bernstein et al. 1992; Fowble et al. 2001; Trentham-Dietz et al. 2007a; Knight et al. 2009; Li et al. 2009a), primarily over the past decade, as the number of women who have survived breast cancer has steadily increased and there has been a growing interest in modifiable risk factors for this disease. Cigarette smoking has been examined as one

of the primary behavioral risk factors, along with alcohol consumption, obesity, and use of oral contraceptives. In a review by Chen and colleagues (1999) of the 16 studies they examined, 3 included cigarette smoking as a factor of interest (Kato et al. 1986; Horn and Thompson 1988; Bernstein et al. 1992), but there was no strong evidence of a significant increased risk. These 3 studies, along with 4 reports published in 2001 or later (Fowble et al. 2001; Trentham-Dietz et al. 2007a; Knight et al. 2009; Li et al. 2009a), are summarized in Table 6.20S. Overall, the findings of these 7 studies are inconclusive with regard to the risk of a second primary contralateral breast cancer in smokers. In the largest cohort of women diagnosed with invasive cancer, the findings for both former and current smoking were not significant (Trentham-Dietz et al. 2007a). In the most recently conducted study, which covered a 15-year follow-up period, Li and colleagues (2009a) reported a significant association between cigarette smoking and both a contralateral breast cancer diagnosis (RR = 2.2; 95% CI, 1.2–4.0) and risk of the first primary breast cancer diagnosis (RR = 1.8; 95% CI, 1.1–3.2). Although Knight and colleagues (2009) evaluated a number of smoking measures, including duration, average packs per day, pack-years, and age at initiation, they found little evidence for an association between cigarette smoking and risk of a primary contralateral breast cancer. That study was focused primarily on premenopausal women, whereas in the study by Li and colleagues (2009a) the majority of women (81%) were postmenopausal and diagnosed with ER+ cancer. Taken together, the results for the association between smoking and having a contralateral breast cancer remain inconclusive.

Genetic Susceptibility to Smoking

The 2004 Surgeon General's report summarized eight studies on the smoking-genotype interaction: one on family history (Couch et al. 2001), one on *BRCA1/2* (Brunet et al. 1998), three on *NAT1* and *NAT2* (Ambrosone et al. 1996; Hunter et al. 1997; Millikan et al. 1998), one on *GSTM1* (Ambrosone et al. 1999a), and two on *CYP1A1* (Ambrosone et al. 1995; Ishibe et al. 1998). The report concluded that susceptible subgroups of women could not be "reliably identified" (USDHHS 2004, p. 312). The Cal/EPA (2005) provided descriptive summaries of studies that focused on susceptible subgroups (i.e., determined by family history, genotype, tumor phenotype); the Canadian Expert Panel tabulated data on the interaction between smoking and a number of genotypes and considered the evidence for *NAT2* to be "persuasive" (Collishaw et al. 2009, p. 47); and the 2009 IARC Monograph Working

Group concluded that results from studies of interactions between smoking and genes were “ambiguous, with the possible exception of *NAT2*” (Secretan et al. 2009, p. 1034).

Family History

Having a family history of first-degree relatives with breast cancer is associated with a doubling to tripling of risk for breast cancer (Goldgar et al. 1994; Pharoah et al. 1997; Poole et al. 1999). This risk is further increased in women with benign breast disease and a family history of breast cancer, especially those with atypical hyperplasia (Collins et al. 2006). This finding provides strong evidence for a genetic predisposition to breast cancer and has led to rapidly expanding efforts to identify specific genetic variants that increase such risk. These may be either rare variants with large effects or the joint action of common variants (SNPs) with small effects that modify susceptibility to behavioral or environmental exposures associated with breast cancer. This section considers evidence for heritable genetic susceptibility to smoking as a risk factor for breast cancer.

Most studies on smoking and breast cancer have controlled for family history, but only a few have assessed the interaction of smoking and family history (Couch et al. 2001; Suzuki et al. 2007). Couch and colleagues (2001) reported that among 132 families with three or more incident cases of breast or ovarian cancer in sisters and daughters, ever smokers had an increased risk (RR = 2.4; 95% CI, 1.2–5.1) for breast cancer compared with never smokers. Risk for ever smokers was even higher (RR = 5.8; 95% CI, 1.4–23.9) in 35 families with five or more breast and/or ovarian cancers. Suzuki and colleagues (2007) also reported a significant interaction between a positive family history of cancer and smoking on risk of breast cancer ($p = 0.01$). In comparisons with never smokers who did not have a family history, risk was over four times as high (RR = 4.33; 95% CI, 1.65–11.40) in women with a family history of breast cancer who reported more than 30 pack-years of smoking but only about one and one-half times as high in those with a family history who never smoked (RR = 1.44; 95% CI, 1.21–1.71). In addition, Suzuki and colleagues (2007) found a strong dose-response relationship in smokers who had a family history of breast cancer. Risk for breast cancer was nearly twice as high in women who had such a family history and accumulated 30 or fewer pack-years (RR = 1.95; 95% CI, 1.36–2.81) but more than four times as high in women who had a family history of breast cancer and accumulated more than 30 pack-years (RR = 4.33; 95% CI, 1.65–11.40) in comparisons with women without a family history who did not smoke. In contrast, the study did not find an association between smoking and risk for breast cancer among women without

a family history of breast cancer: fewer than 30 pack-years (RR = 0.98; 95% CI, 0.87–1.10) and 30 or more pack-years (RR = 0.97; 95% CI, 0.72–1.31). These studies provide strong evidence that genetic factors represented by family history of breast cancer modify the risk for that cancer associated with smoking. More studies are needed to replicate this interaction of smoking and family history and to identify underlying genetic mechanisms.

BRCA1/BRCA2

An estimated 5–10% of all diagnosed breast cancer is inherited, with 2–3% involving mutations in one of the tumor suppressor genes *BRCA1* or *BRCA2* (Ashworth et al. 2010). These mutations account for nearly 40–50% of familial breast cancer cases (Chen et al. 2006b; Ashworth et al. 2010), and women with these mutations are at high risk for developing breast cancer, especially at an early age (Chen et al. 2006b). The cumulative incidence of breast cancer is also high for those who carry an inherited *BRCA* mutation, with an estimated lifetime risk of at least 43–46% by age 70 (Chen et al. 2006b), although estimates of 60–80% have been proposed (Ashworth et al. 2010). These estimates have varied considerably depending on the patients selected and patterns of inheritance. As a result, there is considerable inconsistency among reports to date.

Eight studies (Brunet et al. 1998; Ghadirian et al. 2004; Colilla et al. 2006; Gronwald et al. 2006; Nkondjock et al. 2006; Breast Cancer Family Registry (BCFR) 2008; Ginsburg et al. 2009; Moorman et al. 2010) have examined whether carriers of *BRCA1* and *BRCA2* mutations are more susceptible or less susceptible to cigarette smoke than are noncarriers. Terry and Goodman (2006) reviewed four of these studies (Brunet et al. 1998; Ghadirian et al. 2004; Colilla et al. 2006; Gronwald et al. 2006); in the earliest one, Brunet and colleagues (1998) reported inverse associations between breast cancer and accumulating 4 or more pack-years in carriers of *BRCA1* (OR = 0.47; 95% CI, 0.26–0.86) and *BRCA2* genes (OR = 0.39; 95% CI, 0.10–1.49). A subsequent study by the same team of investigators, based on an extended dataset of subjects from 52 centers in 11 countries, failed to replicate this finding (Ghadirian et al. 2004). Overall, risk of breast cancer from smoking in this study was not significantly decreased for carriers of *BRCA1* (OR = 1.09; 95% CI, 0.87–1.33) or *BRCA2* (OR = 0.97; 95% CI, 0.68–1.38), and no trend was observed with lifetime smoking (Ghadirian et al. 2004). However, using a retrospective cohort study design that included a subset of participants from the same study population as in Ghadirian and colleagues (2004), Colilla and colleagues (2006) reported a reduced risk of breast cancer among ever smokers with *BRCA1* mutation (RR = 0.63; 95% CI, 0.47–

0.87) and inverse dose-response relationships for both less than 20 pack-years (RR = 0.72; 95% CI, 0.52–1.00) and 20 or more pack-years (RR = 0.41; 95% CI, 0.23–0.71; *p* trend = 0.0007). The study also reported that women with the *BRCA1* mutation and who also had a specific polymorphism in the *AIB1* (estrogen receptor coactivator) gene who accumulated 20 or more pack-years of smoking had greatly reduced risk (OR = 0.19; 95% CI, 0.07–0.54).

Ginsburg and colleagues (2009) expanded the number of *BRCA1/2* carriers from the study by Ghadirian and colleagues (2004). The reanalysis of the expanded data set revealed no significant association between risk for breast cancer and ever smoking in carriers of *BRCA1* (OR = 1.09; 95% CI, 0.95–1.24) or *BRCA2* (OR = 0.81; 95% CI, 0.63–1.05) (Ginsburg et al. 2009). Carriers of *BRCA1* who were former smokers, however, had a significantly greater risk of breast cancer (OR = 1.27; 95% CI, 1.06–1.50), but no association was found among carriers of *BRCA1* who were current smokers (OR = 0.95; 95% CI, 0.81–1.12). Total lifetime cigarette consumption was significantly and positively associated with breast cancer among carriers of *BRCA1* who were former smokers (*p* trend = 0.007). The study did not find a significant association with former smoking in *BRCA2* carriers, but current smoking had a nonsignificant inverse association (OR = 0.71; 95% CI, 0.50–1.00). Smoking before the age of 18 was not significant in either carrier group: *BRCA1* (OR = 1.11; 95% CI, 0.89–1.18) or *BRCA2* (OR = 0.78; 95% CI, 0.59–1.04).

Results have been inconsistent in other studies. In a matched case-control study in Poland, Gronwald and colleagues (2006) reported no association of smoking with breast cancer for *BRCA1* carriers (OR = 1.10; 95% CI, 0.8–1.5). Nkondjock and colleagues (2006) conducted a nested case-control study in a cohort of 80 French-Canadian families in which *BRCA1/2* was present in 89 breast cancer cases and 48 controls. The study reported no association with 14 or fewer pack-years (OR = 0.86; 95% CI, 0.34–2.21) or more than 14 pack-years (OR = 0.74; 95% CI, 0.31–1.75) of smoking (*p* trend = 0.49). However, the BCFR (2008)—a consortium of research groups in the Australia, Canada, and the United States—obtained different results in their case-control study. That study reported increased risks for current smokers with *BRCA1/2* mutations (OR = 2.08; 95% CI, 1.41–3.06) and in *BRCA1* (OR = 2.33; 95% CI, 1.56–3.47) and *BRCA2* carriers (OR = 2.64; 95% CI, 1.78–3.90). Moreover, in carriers of both mutations, risk of breast cancer increased significantly with duration of smoking (approximately 7% per pack-year; *p* < 0.001). Overall, the cumulative incidence of breast cancer by 50 years of age for those with a *BRCA1* mutation was about 60% in smokers versus 35% in nonsmokers, and for a *BRCA2* mutation it was 35% in smokers compared with 15% in nonsmokers (BCFR 2008).

In a case-only analysis, Moorman and colleagues (2010) reported no significant interactions between ever smoking and *BRCA1* or *BRCA2* status.

Lecarpentier and colleagues (2011) evaluated the association of smoking and breast cancer in the French National *BRCA1/2* carrier cohort. Sixty-five percent of the cohort (863 women) had *BRCA1* mutations and the remainder (474) had *BRCA2* mutations. Among the *BRCA1* carriers, risk was increased among current smokers who reported no alcohol consumption (RR = 2.09; 95% CI, 0.94–4.65) but not among those who reported ever use of alcohol (HR = 0.87; 95% CI, 0.52–1.43). This difference between nonusers and ever users of alcohol was even greater among those with 21 or more pack-years of smoking (RR = 3.29; 95% CI, 1.09–9.95 vs. RR = 0.87; 95% CI, 0.45–1.68). Among *BRCA2* carriers, there was no significant increase in risk of breast cancer for either current (RR = 1.39; 95% CI, 0.73–2.63) or former smokers (RR = 1.18; 95% CI, 0.60–2.33), but risk was significantly higher for women who reported 21 or more pack-years (RR = 2.25; 95% CI, 1.05–4.82).

In summary, studies of effect modification of smoking by *BRCA1* or *BRCA2* on breast cancer have been inconsistent. Two studies reported an inverse association (Brunet et al. 1998; Colilla et al. 2006), four reported no association (Ghadirian et al. 2004; Gronwald et al. 2006; Nkondjock et al. 2006; Moorman et al. 2010), and one reported a significant positive association (BCFR 2008). Two studies (Ginsburg et al. 2009; Lecarpentier et al. 2011) reported positive results for some measures of smoking but these were inconsistent and difficult to interpret. For example, Ginsburg and colleagues (2009) reported a positive association in women with *BRCA1* mutations who were former but not current smokers; there were no associations in women with the *BRCA2* mutation. As noted previously, Lecarpentier and colleagues (2011) reported positive associations only in women with *BRCA1* who reported never using alcohol; risk was only significantly increased in *BRCA2* carriers who reported 21 or more pack-years of smoking. Of note, four of these reports were based on overlapping participant populations and contradictory results (Brunet et al. 1998; Ghadirian et al. 2004; Colilla et al. 2006; Ginsburg et al. 2009).

Carcinogen Metabolism

Researchers have also addressed common polymorphisms with low penetrance and small additive or multiplicative impacts on risk of breast cancer (Pharoah et al. 2002). With regard to smoking, researchers have considered common genetic variants in biologic pathways that regulate the metabolism and detoxification of tobacco-related carcinogens (Ambrosone and Shields 1999b; Coyle

2004). Thus, a growing number of studies have been designed to examine genetic polymorphisms in enzyme systems—such as GST, cytochrome P-450, and NATs.

N-Acetyltransferase Polymorphisms

The strongest evidence to date for genetic susceptibility to smoking and breast cancer has been for the arylamine NATs, which are enzymes involved in both the detoxification and activation of heterocyclic and aromatic amines (carcinogenic compounds found in cigarette smoke) (Hein 2002). The polymorphisms in the genes for the NAT1 and NAT2 enzymes are very complex; as a result, past studies have been subject to misclassification of the metabolic phenotype, with consequent difficulty in detecting and interpreting associations. Since the first consensus nomenclature was published (Vatsis et al. 1995), the classification has become better standardized with continuing updates (University of Louisville 2013). This improvement has reduced bias in assessing the interaction between NAT phenotypes and smoking and has improved comparisons across studies and the derivation of pooled estimates of effects (Deitz et al. 2004). Evidence clearly indicates that polymorphisms in the *NAT2* gene affect the efficiency of the enzyme system in detoxifying carcinogenic amines and that acetylation status (rapid, intermediate, slow, and very slow) is correlated with carcinogen metabolism, resulting in activation or deactivation of xenobiotics (Hein et al. 2000a,b, 2002). In comparisons with rapid acetylator phenotypes, the slow and very slow acetylator phenotypes have been reported to be associated with an increased frequency of DNA adducts, a phenomenon that appears to be due to reduced detoxification of carcinogenic amines (Pfau et al. 1998; Firozi et al. 2002). Although the prevalence of slow acetylator status varies across populations, it has been reported to be as high as 50–60% in some (Wacholder et al. 2000), with evidence for racial/ethnic variation in the frequencies of *NAT2* genotypes (Garcia-Martin 2008). Previous studies of *NAT2* have reported associations with other cancers that may vary due to activation or inactivation of *N*-hydroxylated heterocyclic amines. Slow acetylation increases the risk for bladder cancer and rapid acetylation increases the risk for colon cancer (Abel and DiGiovanni 2008).

Several studies have evaluated the associations of *NAT1* and *NAT2* polymorphisms with breast cancer and many of these have examined interactions with smoking. Only a few studies have examined *NAT1* (Millikan et al. 1998; Krajcinovic et al. 2001; Lee et al. 2003; van der Hel et al. 2003b; Zheng et al. 1999), as the majority of studies have focused on *NAT2*. Even with standardization, continuous updates have been made with the identification of new alleles. Currently, acetylation status is based on

the categorization of rapid activity (*NAT2*4*, *NAT2*12*, *NAT2*13*), slow activity (*NAT2*5*, *NAT2*6*, *NAT2*7*, *NAT2*14*), and intermediate activity (one allele associated with rapid acetylation activity and one with slow activity). Very slow activity is associated with being homozygous for *NAT2*5* (Hein 2009a).

In the mid-1990s, Ambrosone and colleagues (1996) reported that the association between smoking and breast cancer was elevated in women with *NAT2* slow acetylator status, while those with a rapid acetylator status had a non-significant decreased risk. This finding was replicated 12 years later in a meta-analysis and pooled analysis reported by Ambrosone and colleagues (2008) that in total involved 4,889 premenopausal and 7,033 postmenopausal women. Women with a history of ever smoking who were slow acetylators were at increased risk (vs. never smokers) both overall (RR = 1.27; 95% CI, 1.16–1.40) and by menopausal status (RR = 1.34; 95% CI, 1.17–1.53 for postmenopausal and 1.28; 95% CI, 1.09–1.50 for premenopausal) (Table 6.21S). No increased risk was reported in women who were ever smokers and rapid acetylators (RR = 1.05; 95% CI, 0.95–1.17). Risk was further increased in slow acetylators among those with 20 or more pack-years (meta-analysis RR = 1.44; 95% CI, 1.23–1.68), but not in their counterparts who were rapid acetylators (RR = 1.04; 95% CI, 0.87–1.25); this pattern was seen for both premenopausal and postmenopausal women (Table 6.21S). The association was also present for duration of smoking 15 or more years in slow acetylators regardless of menopausal status: premenopausal, RR = 1.35 (95% CI, 1.11–1.65); postmenopausal, RR = 1.40 (95% CI, 1.11–1.76) versus never smokers. Results from the pooled analysis were consistent with the meta-analysis, with an overall RR summary estimate of 1.49 (1.08–2.04) for women with a history of 20 or more pack-years of smoking and the *NAT2* slow acetylator phenotype compared with never active smokers who had the rapid acetylator phenotype. The interaction of *NAT2* genotype with smoking was significant for ever smoking ($p = 0.02$), pack-years of smoking ($p = 0.03$), and duration of smoking ($p = 0.007$) (Ambrosone et al. 2008).

Before the publication from Ambrosone and colleagues (2008), 1 summary review and 1 meta-analysis reported on the interaction of *NAT2* with smoking on risk for breast cancer. Terry and Goodman's (2006) meta-analysis was based on 13 studies and reported an increased risk for breast cancer among postmenopausal women who smoked and were classified as slow acetylators (Table 6.21S). Ochs-Balcom and colleagues' (2007) review of 12 studies also found evidence that *NAT2* modified risk for breast cancer among women who smoked. A recent meta-analysis by Zhang and colleagues (2010) provided results for the association of *NAT2* with breast cancer modified by

smoking rather than modification by *NAT2* of the association of smoking with risk of breast cancer. As such, the estimates from this meta-analysis cannot be compared with previous findings. Zhang and colleagues (2010) extracted data from studies to recalculate ORs for the main effects of *NAT2* and *NAT2* modified by pack-years of smoking, but in doing this, they could not take into account covariates from original analyses for the effect of smoking modified by *NAT2*. Nonetheless, a significant interaction was found. Taken together, the results of these meta-analyses suggest that the *NAT2* genotype modifies the risk for breast cancer in women who smoke. In addition, there is an increased risk of about 40–50% in women who have the *NAT2* slow acetylation phenotype who smoke.

Two studies have been published since the comprehensive meta-analysis from Ambrosone and colleagues (2008). In a case-control study (717 cases and 735 controls) of Hispanic and non-Hispanic White women in New Mexico, Baumgartner and colleagues (2009) reported an interaction between a history of ever smoking and the *NAT2* phenotype that approached significance in non-Hispanic White women only (p for interaction = 0.06). The risk estimate (OR) for ever smokers with the very slow phenotype was 2.57 (95% CI, 1.49–4.41). In this study, risk was increased similarly in former and current smokers with the very slow phenotype. In Germany, Rabstein and colleagues (2010) reported results for a case-control study involving 1,155 cases and 1,143 controls. The study did not find an interaction between smoking and the *NAT2* phenotype, even when results were stratified by ER phenotype.

Finally, a report from the Breast and Prostate Cancer Cohort Consortium (Cox et al. 2011) pooled data for 6,900 cases and 9,903 controls from seven separate studies (CPS-II/1998, NHS-I/1989 and NHS-II/1999, EPIC 1992, Multi-Ethnic Cohort Study/1996, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial/1993, and Women's Health Study/1993). A significant interaction was not found between duration or pack-years of smoking and the *NAT2* acetylation phenotype. Risk of breast cancer was increased in those with more than 20 pack-years of smoking and fast acetylation status, which was defined as a combination of rapid and intermediate phenotypes (OR = 1.24; 95% CI, 1.08–1.42), as well as in slow acetylators (OR = 1.25; 95% CI, 1.11–1.39). Adjustment included a number of covariates, but not the use of alcohol. This report weakens the evidence for *NAT2* as an effect modifier of smoking on the risk of breast cancer.

Cytochrome P-450 Polymorphisms

CYP1A1 and *CYP1B1* are gene-encoding enzymes involved in the metabolism of estradiol and PAHs. Muta-

genic intermediates generated in this pathway can damage DNA (Sillanpaa et al. 2007). The *CYP1A1* gene encodes a Phase I enzyme that contributes to aryl hydrocarbon hydroxylase activity and metabolism of PAHs, which have been detected in both normal and cancerous breast tissues (Terry and Rohan 2002; Masson et al. 2005). *CYP1B1* is involved in estrogen homeostasis in normal breast tissue and is expressed in breast tumors (Rylander-Rudqvist et al. 2003).

Studies have not documented an interaction of smoking and polymorphisms in these *CYP* genotypes on risk for breast cancer. Masson and colleagues (2005) reviewed five studies with data on the interaction of smoking and *CYP1A1* polymorphisms on risk for breast cancer (Ambrosone et al. 1995; Bailey et al. 1998; Ishibe et al. 1998; Taioli et al. 1999; Basham et al. 2001), but only one (Ambrosone et al. 1995) provided evidence for a possible interaction, and a formal statistical test was not conducted in that study. Furthermore, results from these studies are difficult to interpret because of their small samples and differences in reference groups, categories of smoking, and definition of interactions. Terry and Goodman (2006) conducted a meta-analysis of four studies (Ambrosone et al. 1995; Ishibe et al. 1998; Basham et al. 2001; Li et al. 2004), three of which (all but Li et al. 2004) were reviewed by Masson and colleagues (2005). The summary estimate among smokers with the wild-type genotype (OR = 1.3; 95% CI, 1.0–1.6) did not differ significantly from those with variant alleles (OR = 1.2; 95% CI, 0.6–2.1), suggesting no interaction.

Studies of the interaction between *CYP1B1* polymorphisms and smoking on risk for breast cancer have produced mixed results. Saintot and colleagues (2003) reported increased risk for breast cancer among former smokers (OR = 1.33; 95% CI, 0.59–2.96) and current smokers (OR = 2.32; 95% CI, 1.00–5.38) with the *CYP1B1* *LEU/LEU* genotype compared with nonsmokers with *VAL* alleles. In contrast, Rylander-Rudqvist and colleagues (2003) reported no association between smoking and any *CYP1B1* genotype on risk for breast cancer. The case-control study conducted by Sillanpaa and colleagues (2007) reported unstable findings because of small samples in some strata: for example, risk was increased significantly among smokers who consumed 1–9 cigarettes per day and (a) were carriers of the *CYP1B1* *VAL* allele (OR = 2.63; 95% CI, 1.07–6.46) or (b) had the *VAL/VAL* genotype (OR = 5.09; 95% CI, 1.30–19.89; p trend = 0.005), but these increased risks were not observed in women who smoked more than 10 cigarettes per day. Results for duration of smoking and pack-years of smoking were also contradictory.

Sillanpaa and colleagues (2007) also reported a significant increased risk for breast cancer in smokers with the *CYP1B1* *VAL* allele who were *NAT2* slow acetylators

(OR = 2.46; 95% CI, 1.11–5.45), suggesting a potential three-way interaction between smoking, *CYP1B1*, and *NAT2*. Van Emburgh and colleagues (2008b) reported a significant interaction ($p = 0.02$) between smoking and the *CYP1B1 119S* allele on risk for breast cancer in African Americans but not in Whites. Taken together, these studies do not provide strong or consistent evidence for modification of risk for breast cancer from smoking by polymorphisms in genes for the CYP enzyme system.

Glutathione S-transferases

GSTs are Phase II enzymes that metabolize and detoxify endogenous and exogenous substances, including tobacco smoke carcinogens—specifically PAHs (Terry and Goodman 2006). DNA adducts are more common in smokers with breast cancer who have certain polymorphisms in genes for the GST enzymes (van der Hel et al. 2003b). The GST enzyme system contains eight families of genes, and polymorphisms have been described in several of these families—mainly mu (M1), theta (T1), and pi (P1) (Vogl et al. 2004; Terry and Goodman 2006). *GSTM1* and *GSTT1* are deletion (*null*) polymorphisms that result in the absence of protein expression.

Terry and Goodman (2006) performed a meta-analysis of seven studies (Ambrosone et al. 1995; Garcia-Closas et al. 1999; Millikan et al. 2000; Zheng et al. 2002a,b; van der Hel et al. 2003b, 2005) that investigated the potential modification by *GSTM1* and *GSTT1* of the association between smoking and risk for breast cancer. Six studies were population-based or nested case-control designs and one was a case-cohort study. Using categories for longest duration of smoking, the RRs from the meta-analysis were 1.4 (95% CI, 1.1–1.9) for *GSTM1null* versus 1.10 (95% CI, 0.80–1.40) for *GSTM1present*, suggesting possible effect modification. In contrast, smoking was associated with breast cancer regardless of *GSTT1* genotype: *GSTT1null* (meta-RR = 1.20; 95% CI, 0.90–1.70) and *GSTT1present* (meta-RR = 1.30; 95% CI, 1.10–1.60).

Several studies have examined the main effects of *GST* polymorphisms on risk for breast cancer stratified by smoking status. Although these studies did not provide estimates by genotype for modification of the association between smoking and breast cancer, many included tests for interaction that can be interpreted as evidence that a polymorphism alters this association. Vogl and colleagues (2004) pooled results from seven case-control studies (Bailey et al. 1998; Maugard et al. 1998; Nedelcheva et al. 1998; Ambrosone et al. 1999a; Zhao et al. 2001; da Fonte de Amorim et al. 2002; Zheng et al. 2002b) and found no evidence of significant interaction between smoking and *GSTM1*, *GSTT1*, or *GSTP1* polymorphisms. A study by

Mitrunen and colleagues (2001a), which was not included in the pooled analysis by Vogl and colleagues (2004), did not detect any interaction between a history of smoking and either *GSTM1*, *GSTM3*, *GSTP1*, or *GSTT1* genetic polymorphisms. Subsequent studies have not reported significant interactions between *GST* polymorphisms and smoking on risk for breast cancer (Linhares et al. 2005; Ahn et al. 2006; Olsen et al. 2008; Van Emburgh et al. 2008b; McCarty et al. 2009; Andonova et al. 2010). Thus, with the possible exception of *GSTM1*, the evidence to date does not support modification of the breast cancer–smoking association by polymorphisms in the GST enzyme system.

Sulfotransferase 1A1

SULT enzymes activate or inactivate PAHs and heterocyclic amines from cigarette smoke through sulfonate conjugation. A common polymorphism (*ARG213HIS*) in SULT1A1 results in reduced enzyme activity and efficiency of this pathway (Terry and Goodman 2006). Only three studies to date have examined interactions between this polymorphism and smoking on risk for breast cancer (Saintot et al. 2003; Lilla et al. 2005; Sillanpaa et al. 2005b). The case-only study by Saintot and colleagues (2003) suggested interactions between the *HIS* allele and both duration of smoking (>20 years) (OR = 1.71; 95% CI, 0.97–3.03) and intensity of smoking (>5 cigarettes/day) (OR = 1.65; 95% CI, 0.97–2.80). In contrast, two subsequent case-control studies did not find evidence of an interaction between SULT1A1 and smoking (Lilla et al. 2005; Sillanpaa et al. 2005b).

Oxidative Metabolism Genotypes

Smoking is associated with increased oxidative stress (Pryor and Stone 1993), and superoxide dismutase 2 (SOD2) is a mitochondrial enzyme that protects against oxidative stress. A common polymorphism in the gene for SOD2 reduces the activity of this enzyme and is reportedly associated with several cancers, including breast cancer (Millikan et al. 2004; Gaudet et al. 2005). Terry and Goodman (2006) reviewed four case-control studies on the modification of risk for breast cancer by smoking and SOD2 (Mitrunen et al. 2001b; Millikan et al. 2004; Tamimi et al. 2004; Gaudet et al. 2005); in one of the studies, Millikan and colleagues (2004) reported a significant increased risk of breast cancer for smoking duration of more than 20 years in women homozygous for the variant *ALA* allele (OR = 1.5; 95% CI, 1.0–2.2). However, an increased risk for ever smokers who were homozygous for the wild-type *VAL* allele (OR = 2.6; 95% CI, 1.1–6.3) was reported (as calculated by Terry and Goodman [2006] for

the study by Gaudet and colleagues [2005]). Results from the other two studies were null. The overall meta-RR estimate for the four studies was 1.5 (95% CI, 1.1–2.1). Only two other case-control studies have been published since this review (Slanger et al. 2006; Kostyrykina et al. 2009); neither found significant interactions between SOD2 and smoking or main effects of SOD2 or smoking on risk for breast cancer.

DNA Repair Genes

Terry and Goodman (2006) reviewed seven studies with data on modification of risk for breast cancer by smoking and DNA repair genotypes, including polymorphisms in *XRCC1*, *XPD*, and *MGMT*. Five studies, which included two or three different polymorphisms in *XRCC1* (*ARG³⁹⁹GLN*, *ARG¹⁹⁴TRP*, AND *ARG²⁸⁰HIS*) and widely different smoking exposures (ever smoking, duration >20 years, >5 pack-years of smoking), produced inconsistent results (Duell et al. 2001; Metsola et al. 2005; Patel et al. 2005; Shen et al. 2005a; Pachkowski et al. 2006). The meta-analytic summary estimate for smoking exposure was significant only for women homozygous for *194 ARG/ARG*. Two studies of the *XPD LYS751GLN* polymorphism reported nonsignificant increased risks for smokers with the *GLN/GLN* genotype (as calculated by Terry and Goodman [2006] for the studies by Terry and colleagues [2004] and Metsola and colleagues [2005]). A study by Shen and colleagues (2005b) reported increased risk in heavy smokers with *MGMT LEU84PHE* and *ILE143VAL* polymorphisms.

In the NHS-I cohort, Han and colleagues (2003) found no evidence for effect modification of smoking by any of four SNPs (*ARG¹⁹⁴TRP*, *C26602T*, *ARG³⁹⁹GLN*, and *GLN⁶³²GLN*) in *XRCC1*. Subsequently, Han and colleagues (2004) reported no interaction between smoking and SNPs in the *XRCC2*, *XRCC3*, and *LIG IV* genes, and Han and colleagues (2006) did not report such an interaction in the *MGMT* gene. Shore and colleagues (2008) reported an interaction between smoking and a SNP in the *XPC* gene that approached significance ($p = 0.08$) in the NYU Women's Health Study. Mechanic and colleagues (2006) found that the combination of smoking and four or more SNPs in several nucleotide excision repair genes (*XPD*, *XPC*, *RAD23B*, *XPG*, *XPF*, and *ERCC6*) significantly modified the risk for breast cancer in African American, but not White, women. Similarly, Metsola and colleagues (2005) found strong evidence for modification of the association between smoking and the combination of two or more SNPs in *XRCC1* and *XPD* on the risk for breast cancer. Future studies should emphasize interactions between smoking and combinations of SNPs within and across genes (Neumann et al. 2005).

Since 2000, several studies have evaluated SNPs in the nuclear receptor coactivator *AIB1* gene (Colilla et al. 2006), the *IGHMBP2* gene (Shen et al. 2006), the *A-T* gene (Swift and Lukin 2008), the *NOS3* and *MPO* genes (Yang et al. 2007), and the *mEH* gene (de Assis et al. 2002) for interaction with smoking on risk of breast cancer. However, the results have been either null or indicated only weak associations. None of these studies have been replicated to date. Additionally, three studies evaluated the association between smoking and *p53* mutational status as a measure of apoptosis (Conway et al. 2002; Furberg et al. 2002; Gaudet et al. 2008). A recently published analysis of more extensive data from the Long Island Breast Cancer Study Project suggested that cigarette smoking and passive smoking were more strongly associated with *p53*-negative cancer (Mordukhovich et al. 2010), which contrasts with results reported by Conway and colleagues (2002), Van Emburgh and colleagues (2008a), and an earlier analysis of the Long Island study (Gaudet et al. 2008).

Genetic Susceptibility—Summary

The epidemiologic studies conducted to date have not established clear or consistent evidence for modification of the association between smoking and breast cancer by genes that influence susceptibility to tobacco-related carcinogens. The published reports support only genetic variation in *NAT2* as a potential effect modifier of the association of breast cancer with smoking, although this finding has been weakened by the recent report of Cox and colleagues (2011). Unfortunately, a variety of limitations have affected these studies. First, many have been too small to provide adequate statistical power for detecting interactions between smoking and low-frequency genotypes. Terry and Goodman (2006) reported that statistical power was less than 80% for detecting a risk estimate of at least 2.0 for breast cancer for the majority (68%) of studies in their review. In addition, the definitions of smoking exposure have varied widely across studies, making it difficult to combine estimates in meta-analyses. Most studies have tested only a limited number of selected SNPs in specific groups of candidate genes, targeting mainly those that influence carcinogen metabolism, oxidative stress, or DNA repair. Not all of these studies have established the functionality of SNPs. Only a few studies have analyzed interactions of smoking with haplotype combinations of SNPs within or across genes. Investigators will likely continue to examine this important area of research by combining genomewide association studies with gene expression assays to identify functional gene variants that modify susceptibility to smoking (Chung et al. 2010).

Summary and Review of Active Cigarette Smoking

The 2004 Surgeon General's report on active cigarette smoking concluded that there was (a) no consistent evidence for an association between active smoking and breast cancer, and that (b) subgroups of women could not be reliably identified that were at increased risk of breast cancer due to smoking. Since the previous report, 12 cohort and 30 case-control studies have been published on the association of smoking with breast cancer. Several large cohort studies now provide consistent evidence for a significant, although weak, positive association. While the findings from the case-control studies are more variable, when considered together the results are in keeping with those from the cohort studies. The meta-analyses confirm a weak but statistically significant, positive association of smoking with risk of breast cancer. The estimates for active smoking tend to be higher when based on data from case-control studies than on data from cohort studies; but there is greater heterogeneity among estimates from case-control studies. Sensitivity analyses reveal that this heterogeneity is largely related to issues in the design or analysis of certain studies. When these studies are removed, the summary estimates from the case-control studies converge to agreement with those from the cohort studies. The sensitivity analyses also suggest that the positive association of smoking with breast cancer is statistically robust.

Ever smoking is associated with a significant increase in RR of about 10% (Table 6.17S). The magnitude of the association appears to be slightly stronger for current smoking (12%) than for former smoking (9%). It is increased by 16% for duration of 20 or more years, 13% for smoking 20 or more cigarettes per day, and 16% for accumulating 20 or more pack-years. There is no clear evidence that earlier age at initiation of smoking (8%) or smoking before first pregnancy (10%) is associated with a greater risk of breast cancer than is ever smoking. There is evidence, based on the most conservative combined study design estimates, that among ever smokers, premenopausal women have a slightly higher increase in risk than postmenopausal women, 17% versus 7%, respectively (Table 6.18S). It remains to be established whether smoking is more strongly associated with a particular tumor phenotype. There is no consistent evidence to date that subpopulations of women with genetic susceptibility to tobacco-related carcinogens (even *NAT2*, given the most recent report by Cox and colleagues [2011]), can be reliably identified as being at increased risk for breast cancer.

The use of a no active/no passive exposure referent appears to have a small impact on most summary estimates, but this can be difficult to interpret because it results in a very small reference group and a loss of statistical power. Future studies need to determine whether statistical adjustment for exposure to passive smoking is adequate. This may require stronger techniques and methods of measuring exposure to secondhand smoke.

Major Summary Points for Active Smoking

1. Based on 22 cohort reports published prior to 2012 and 27 case-control reports published from 2000–2011, evidence suggests that a history of ever smoking is associated with an increase in the RR for breast cancer by an average of 10%; long duration of smoking (20 or more years), greater number of cigarettes smoked per day (20 or more), and more pack-years of smoking (20 or more) significantly increase risk for breast cancer by 13–16%, depending on study design and the exclusion of studies with design or analysis issues.
2. Studies have not clearly determined whether either early age at smoking initiation or smoking before first pregnancy is associated with increased risk for breast cancer over and above the risk due to ever smoking.
3. Studies have not clearly determined whether the use of a restricted no active/no passive exposure reference group or adjustment for exposure to passive smoking meaningfully alters or clarifies the association between smoking and risk for breast cancer.
4. The extent to which the use of alcohol confounds the association between smoking and risk for breast cancer remains uncertain and should be considered in relation to the duration, dose, and timing of smoking.
5. There is emerging evidence to suggest that the risk of breast cancer from smoking may be greater in premenopausal than postmenopausal women, 17% versus 7%, or a relative difference of 9%.
6. There is insufficient evidence to conclude that the risk of breast cancer from smoking differs between women diagnosed with ER+ tumors and those diagnosed with ER– tumors.

7. With the possible exception of the polymorphism in the NAT2 carcinogen metabolism pathway, subgroups of women who are at increased risk of breast cancer because of the interaction between smoking and genotype cannot be identified reliably.

Exposure to Secondhand Smoke and Risk for Breast Cancer

Compared with directly inhaled tobacco smoke or mainstream smoke, the evidence indicates that undiluted sidestream smoke, the major contributor to secondhand smoke (passive smoke, involuntary smoking, environmental tobacco smoke [ETS]), contains higher levels of several substances considered to be carcinogenic, cocarcinogenic, or toxic—including benzene, formaldehyde, catechol, and *N*-nitrosamines (IARC 2004; USDHHS 2010). Measuring exposure to secondhand smoke for assessment of cancer risk poses challenges, however, because an ideal comprehensive assessment should address duration of exposure, dosage (exposure time, number of people who smoke in the immediate environment, number of cigarettes smoked by smokers, ventilation), location of exposure (home, workplace), time period of exposure (childhood, adulthood), and method of assessing exposure (self-report, biologic specimen). Other relevant issues include the pervasiveness of secondhand smoke in the environment, particularly in the past in the United States and some other Western countries, changes in intensity over time, measurement error, and information bias that may dilute estimates of association (Kawachi and Colditz 1996). Methodologic issues in investigating secondhand smoke and disease risk were addressed in the 2006 report of the Surgeon General. Despite strong evidence from cotinine levels of declining exposure to secondhand smoke in the United States, there is no level of exposure considered to be risk free (USDHHS 2006), and high levels of exposure persist for some groups (Chen et al. 2010a).

Exposure to secondhand smoke has been investigated as a risk factor for breast cancer over nearly three decades. Sandler and colleagues (1985a) first evaluated the association between passive smoking exposure and breast cancer in the mid-1980s in a small hospital-based case-control study in North Carolina. In the early 1990s, Wells (1991) analyzed data from Hirayama's large Japanese cohort study (Hirayama 1984, 1990), which was initiated in 1965. Both studies found nonsignificantly increased

risks for breast cancer. These and several subsequent studies had limitations, however, such as mixing incident and prevalent cases with breast cancer deaths; using proxy reports; having limited data for duration, dose, location, and timing of exposure; and adjusting inadequately for relevant confounders. Palmer and Rosenberg (1993) cited only the reports from Hirayama (1984), Sandler and colleagues (1986), and Wells (1991); the latter was a re-analysis of the data from the studies by Hirayama (1984) and Sandler and colleagues (1985a). They concluded that “so little research” had been conducted that it was “not possible to reach any conclusions” (Palmer and Rosenberg 1993, p. 152).

Several meta-analyses and monographs about passive smoking and breast cancer have been published or released, some not long before or after the 2006 Surgeon General's report (Khuder and Simon 2000; Khuder et al. 2001; Morabia 2002a; Cal/EPA 2005; Johnson 2005; Lee and Hamling 2006; Nagata et al. 2006; Pirie et al. 2008; Collishaw et al. 2009; Secretan et al. 2009). The authors of these studies have drawn markedly different interpretations and conclusions, despite considerable overlap among some of these reports in the studies reviewed and evaluated through meta-analysis.

Khuder and Simon (2000) published one of the first systematic reviews of passive smoking and risk for breast cancer. That review examined 11 reports (3 cohort and 8 case-control) that were published between 1984 and 2000 (Hirayama 1984; Sandler et al. 1986 [based on Sandler et al. 1985a]; Smith et al. 1994; Morabia et al. 1996; Johnson et al. 1998, 2000; Jee et al. 1999; Lash and Aschengrau 1999; Liu et al. 2000; Marcus et al. 2000; Wartenberg et al. 2000). Two of the three cohort studies examined breast cancer mortality (Hirayama 1984; Wartenberg et al. 2000), and one was reported as an abstract (Johnson et al. 1998). Results were summarized using the random-effects model. The summary estimate of the RR for ever being exposed to secondhand smoke was 1.41 (95% CI, 1.14–1.75). Based on their results, Khuder and Simon (2000) suggested a “possible weak association between passive smoking and breast cancer” (p. 1117) and that more studies were needed. Morabia (2002a) also reviewed the associations between passive smoking, as well as active smoking, and breast cancer. This review considered most of the same studies assessed by Khuder and Simon (2000) but did not calculate a summary estimate. Instead, Morabia (2002a) noted that ORs were greater than 1.5 in 5 of the 11 case-control studies he reviewed and emphasized the importance of separating passive from active exposures in future studies.

The 2004 IARC monograph reviewed results from 5 cohort and 10 case-control studies and concluded that the “collective evidence on breast cancer risk associated with involuntary exposure of never smokers to tobacco smoke is inconsistent” (p. 1410). The monograph emphasized results from the NHS-I (Egan et al. 2002) and the CPS-II (Wartenberg et al. 2000), noting that these large cohort studies “provided no support for a causal relation between involuntary exposure to tobacco smoke and breast cancer in never smokers,” that the “lack of a positive dose-response also argue[d] against a causal interpretation of these findings,” and that “the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking” (IARC 2004, p. 1410).

In contrast, a report from 2005 about secondhand smoke as a toxic air contaminant (Cal/EPA 2005), which was also summarized by Miller and colleagues (2007), included an extensive section about breast cancer in which it noted that “the weight of evidence (including toxicology of ETS [environmental tobacco smoke] constituents, epidemiological studies, and breast biology) is consistent with a causal association between ETS exposure and breast cancer in younger, primarily premenopausal women” (Cal/EPA 2005, p. ES8). The pooled RR estimate was 1.68 (95% CI, 1.31–2.15), based on a meta-analysis of 14 studies reporting risk for breast cancer among never-smoking premenopausal women who reported exposure to passive smoking. However, the overall test for heterogeneity was significant ($p = 0.001$), suggesting substantial inconsistency across studies. When the analysis was restricted to 5 studies (Smith et al. 1994; Morabia et al. 1996; Zhao et al. 1999; Johnson et al. 2000; Kropp and Chang-Claude 2002) with what was considered “better exposure assessment” (Cal/EPA 2005, p. ES-3), the pooled RR estimate was 2.20 (95% CI, 1.69–2.87), and a test for heterogeneity was not significant ($p = 0.354$).

The Cal/EPA report differed from the 2006 Surgeon General's report with respect to two studies. The Cal/EPA excluded the study by Liu and colleagues (2000) because the panel found that the results were difficult to interpret as the study was clinic based and small ($n = 186$ cases) and reported results based on a passive smoking index (number of smokers times smoke exposure levels, defined as light, medium, or very heavy). The estimate of breast cancer risk for adult home exposure based on this index was $RR = 4.07$ (95% CI, 2.21–7.50) (Liu et al. 2000). However, the 2006 Surgeon General's report included estimates from Liu based on number of smokers exposed to smoke in

the workplace and on levels of at-home smoke exposure by number of cigarettes smoked per day (≤ 2 , 3–9, 10–19, ≥ 20) (Liu et al. 2000). In contrast to the estimated quadrupling of risk in the Cal/EPA report, the pooled risk estimate for adult home exposure was 1.47 (95% CI, 0.74–2.95) (Liu et al. 2000); this estimate was used in the meta-analysis in the 2006 Surgeon General's report. Additionally, the 2006 Surgeon General's report included the study by Bonner and colleagues (2005) that was published after the period of inclusion for studies in the Cal/EPA report had passed. This study reported a significant inverse association for exposure at the workplace (calculated pooled OR = 0.79; 95% CI, 0.65–0.96) but no significant effect for exposure at home (calculated pooled OR = 1.16; 95% CI, 0.96–1.41).

In a meta-analysis by Johnson (2005) of the association between passive and active smoking and breast cancer, the analysis for passive smoking was based on 19 studies (7 cohort and 12 case-control) that met specific quality criteria for study design and exposure measurement (Hirayama 1984; Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Millikan et al. 1998; Jee et al. 1999; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Delfino et al. 2000; Johnson et al. 2000; Wartenberg et al. 2000; Nishino et al. 2001; Egan et al. 2002; Kropp and Chang-Claude 2002; Shrubsole et al. 2004; Gammon et al. 2004a; Reynolds et al. 2004b; Hanaoka et al. 2005). These studies were mostly the same as those included in the 2005 Cal/EPA report and the 2006 Surgeon General's report. The summary pooled risk estimate for all 19 studies using the broadest definition of passive smoking was 1.27 (95% CI, 1.11–1.45; test for heterogeneity $p < 0.001$). The broadest definition of passive smoke exposure in most studies included the following: exposure from any source, including husband's smoking history; years smoked by spouse; lifetime residential childhood exposure; workplace exposure; and parental exposure. As in the Cal/EPA report, 5 case-control studies strongly influenced the summary of pooled risk estimate (Smith et al. 1994; Morabia et al. 1996; Zhao et al. 1999; Johnson et al. 2000; Kropp and Chang-Claude 2002), because they were considered to have the most complete assessments of exposure. The summary pooled risk estimate (RR) for these 5 studies was 1.90 (95% CI, 1.53–2.37). In contrast, the summary RR was 1.16 (95% CI, 0.95–1.42) for the remaining 7 case-control studies (those considered to have less complete assessments of exposure). The summary estimate for the 7 cohort studies was 1.06 (95% CI, 0.97–1.16). Johnson (2005) also calculated summary estimates for risk of breast cancer among premenopausal women by using data from 14 of the 19 studies. The overall summary estimate was higher for premenopausal women ($RR = 1.68$; 95% CI, 1.33–2.12; $p = 0.002$ for heterogeneity) than for all women

and was highest for the 5 studies (as a group) considered to have the most complete assessment of exposure (RR = 2.19; 95% CI, 1.68–2.84). Johnson (2005) did not calculate summary estimates by timing, source, duration, or dose of exposure to passive smoking. The author concluded that “studies with thorough passive smoking exposure assessment implicate passive and active smoking as risk factors for premenopausal breast cancer” but that more cohort studies with thorough exposure assessments were needed (Johnson 2005, p. 619).

Lee and Hamling (2006) conducted a systematic review and meta-analysis of 22 studies (13 case-control, 8 prospective cohort, and 1 nested case-control) involving nonsmoking women that were published through June 2005. RR estimates that adjusted for the greatest number of confounding variables for exposure to secondhand smoke at home, at the workplace, during childhood, during adulthood, or during lifetime were used when available. Results of the meta-analysis included several subgroup variables from the studies—including menopausal status ($n = 11$), the woman’s age or the age of husband ($n = 4$), and genotype ($n = 5$). Results were also stratified by location, source, or timing of exposure: home ($n = 19$), workplace ($n = 5$), childhood ($n = 9$), spouse ($n = 8$), and lifetime ($n = 6$). A sensitivity analysis removed studies that adjusted for fewer than nine covariates but resulted in little inflation of the RR—from 1.23 (95% CI, 1.03–1.45) to 1.28 (95% CI, 1.07–1.53). Overall, this meta-analysis was similar to the one reported in the 2006 Surgeon General’s report, although it excluded the study by Zhao and colleagues (1999) and did not include the study by Bonner and colleagues (2005), which was reported after its publication. The review by Lee and Hamling (2006) also included two abstracts (Rookus et al. 2000; Woo et al. 2000) and a cohort study reported on by Gram and colleagues (2005). The results were similar to those reported in the 2006 Surgeon General’s report: a nonsignificant summary estimate based on 9 cohort studies (RR = 1.02; 95% CI, 0.93–1.10), a significant summary estimate based on 13 case-control studies (RR = 1.28; 95% CI, 1.07–1.53), and a significant increased risk for breast cancer among premenopausal women based on 10 studies (RR = 1.54; 95% CI, 1.16–2.05), but with significant heterogeneity ($p < 0.01$). Additionally, risk estimates for small studies (< 500 cases) were higher (RR = 1.27; 95% CI, 1.03–1.57) and showed significant heterogeneity compared with large studies (≥ 500 cases) (RR = 1.01; 95% CI, 0.93–1.09). Lee and Hamling (2006, p. 1,068) noted that “one cannot confidently conclude, based on the evidence available, that ETS exposure increases risk in nonsmokers.”

Pirie and colleagues (2008) conducted a meta-analysis of 8 cohort and 17 case-control studies on exposure

to secondhand smoke. The analysis included all 21 studies from the 2006 Surgeon General’s report and 4 other studies—2 case-control studies (Lissowska et al. 2006; Roddam et al. 2007), 1 cohort study on mortality (Sagiv et al. 2007), and results from the Million Women Study, a cohort study in the United Kingdom (Pirie et al. 2008). Overall, data reported for the cohort studies indicated no association with breast cancer (RR = 0.99; 95% CI, 0.93–1.05), but data reported for the case-control studies noted a significant association (OR = 1.21; 95% CI, 1.11–1.32; $p_h < 0.0002$). When based on data for the cohort studies, results reported by Pirie and colleagues (2008) for exposure to passive smoking as a child and as an adult were identical (RR = 1.00; 95% CI, 0.94–1.07). Analyses were not stratified on menopausal status or source or location of exposure, as they were in the 2006 Surgeon General’s report. Conclusions were strongly influenced by results from the cohort studies: “In aggregate little or no adverse effect on the risk of breast cancer” was evident, and the results based on the case-control studies “appear[ed], in aggregate, to be misleading” (Pirie et al. 2008, p. 1,077).

The 2009 Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk—based primarily on its updated review of four studies published in 2005 or later (Bonner et al. 2005; Lissowska et al. 2006; Roddam et al. 2007; Pirie et al. 2008), previous reports by the Cal/EPA, and the 2006 Surgeon General’s report—concluded that “the relationship between secondhand smoke and breast cancer in younger, primarily premenopausal women is consistent with causality” but determined that evidence was insufficient for a conclusion on risk of postmenopausal breast cancer (Collishaw et al. 2009, p. 57). In its special report from November 2009 that included an assessment of exposure to secondhand smoke, IARC concluded that “evidence for female breast cancer remains inconclusive” (Secretan et al. 2009, p. 1,033).

Conclusions from Previous Surgeon General’s Reports

The 1986 Surgeon General’s report was the first to offer a conclusion on passive smoking and cancer, but given available evidence it addressed only lung cancer (USDHHS 1986). This report also concluded that the effects of passive exposure were likely not greater than those effects seen for smokers, echoing a similar conclusion of IARC Monograph 38 of WHO (IARC 1986).

The 2006 Surgeon General’s report concluded that the evidence on exposure to secondhand smoke was “suggestive but not sufficient to infer a causal relationship”

with risk for breast cancer (p. 480), based on a review of 7 prospective cohort studies (Hirayama 1984, reanalyzed by Wells [1991]; Jee et al. 1999; Wartenberg et al. 2000; Nishino et al. 2001; Egan et al. 2002; Reynolds et al. 2004b; Hanaoka et al. 2005) and 15 case-control studies (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Millikan et al. 1998; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Delfino et al. 2000; Johnson et al. 2000; Liu et al. 2000; Marcus et al. 2000; Kropp and Chang-Claude 2002; Shrubsole et al. 2004; Gammon et al. 2004a; Bonner et al. 2005). In the 2006 report, pooled risk estimates were derived for all women and stratified by menopausal status and categories related to timing (childhood, adulthood), source (spouse), and location (home, workplace) of exposure. The overall risk estimate (RR = 1.20; 95% CI, 1.08–1.35) was based on the most comprehensive measure of exposure to secondhand smoke. Data from cohort studies indicated no association (RR = 1.02; 95% CI, 0.92–1.13) with breast cancer, but the summary estimate from case-control data showed a significant association (OR = 1.40; 95% CI, 1.17–1.67). The association was particularly strong for premenopausal women (OR = 1.64; 95% CI, 1.25–2.14), based on estimates from 2 cohort studies (Reynolds et al. 2004b; Hanaoka et al. 2005) and 9 case-control studies (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Millikan et al. 1998; Delfino et al. 2000; Johnson et al. 2000; Gammon et al. 2004a; Shrubsole et al. 2004; Bonner et al. 2005). The review did not find an association for postmenopausal women (OR = 1.00; 95% CI, 0.88–1.12) based on the same 2 cohort studies (Reynolds et al. 2004b; Hanaoka et al. 2005) and 7 of the 9 case-control studies (Sandler et al. 1985a; Millikan et al. 1998; Delfino et al. 2000; Johnson et al. 2000; Gammon et al. 2004a; Shrubsole et al. 2004; Bonner et al. 2005). The review identified several issues related to these results—including the significant heterogeneity among studies, especially for the case-control studies; the potential for selection and information biases; the lack of consistency between findings for active cigarette smoking and those for exposure to secondhand smoke; and biologic plausibility.

In summary, several reviews and meta-analyses have been conducted to date—including reports by IARC, the Cal/EPA, the Canadian Expert Panel, Surgeon General's reports, and several groups of investigators (Khuder and Simon 2000; Johnson 2005; Lee and Hamling 2006; Pirie et al. 2008). These reports have reached different conclusions about the presence and magnitude of association between passive exposure to smoke and breast cancer despite considerable overlap in the studies reviewed and analyzed. Some of the difference in interpretation is related to the relative weight given by the authors of the reviews and meta-analyses to results from case-control

versus cohort studies. The majority of case-control studies have reported positive associations, with summary estimates (RRs) ranging from 1.2–1.9 depending on the studies included. Results from cohort studies have mostly been null. Compared with cohort studies, case-control studies often include more extensive and rigorous assessments of exposure—including detailed information for timing (childhood, adulthood), location (home, workplace), source (parent, spouse, other), duration, and dose—but these studies are more susceptible to information bias and generally considered less reliable. In addition, most of the case-control studies published before 2006 were small (<100 cases) or moderate (<500 cases) in size and had imprecise estimates. The likelihood of extreme estimates is increased in small studies and leads to significant heterogeneity across studies. In any case, all of the previous reviews have concluded that more and larger studies are needed, particularly those with cohort designs, with more detailed and extensive assessments of exposure.

Cohort Studies

The 2006 Surgeon General's report covered 21 studies, identified through 2005, on the health consequences of involuntary exposure to tobacco smoke. From 2006–2011, 7 cohort studies have evaluated exposure to passive smoking (Table 6.22S). As part of the Norwegian-Swedish cohort, Gram and colleagues (2005) followed 102,098 women, 30–50 years of age, for an average of 8–9 years (1991/1992–2000) and ascertained 1,240 incident cases of breast cancer among current or former smokers and never smokers. Exposure to passive smoking at home was assessed from self-reports of living with a smoker, either currently or during childhood. In a multivariate model based on 1,130 cases with complete data, the RR for breast cancer among women who never smoked but reported exposure to passive smoking (n = 24,030) was 1.21 (95% CI, 0.98–1.50) in a comparison with never smokers who reported no exposure to passive smoking (n = 12,743). The study adjusted for multiple covariates—including age, menopausal status, parity, age at birth of first child, use of hormones, BMI, and use of alcohol.

In the Million Women Study, Pirie and colleagues (2008) ascertained 2,344 incident cases in a cohort of 210,647 women, 50–64 years of age, who never smoked, had complete data for passive smoking exposure, and were followed for an average of 3.5 years. Exposure to passive smoking was based on self-reports of living with a parent who smoked at the time the participant was born and when she was 10 years of age, and of currently living with a partner who smoked. Only 17% of women reported not being exposed to passive smoking during childhood or

adulthood, leaving a relatively small reference group with no active/no passive exposure for the analyses. The overall RR was 0.99 (95% CI, 0.93–1.05) for any passive exposure. After adjusting for relevant covariates, including use of alcohol, the study found no increased risk of breast cancer from exposure during childhood (RR = 0.96; 95% CI, 0.88–1.05) or adulthood (RR = 1.02; 95% CI, 0.89–1.16).

Lin and colleagues (2008) reported findings from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk based on 208 incident breast cancer cases in 34,401 women, 40–79 years of age, who were followed an average of 11–13 years. The study assessed exposure to passive smoking based on self-reports—including the estimated frequency of exposure (either sometimes or almost every day)—as adults at home and in public places, and during childhood. There were 196 cases among 32,023 never-smoking women, but the numbers in various analyses ranged from 140–178. After adjusting for relevant covariates, including use of alcohol, RRs for exposure during adulthood at home and in public places almost every day were less than 1.0 (RR = 0.71; 95% CI, 0.48–1.05 and RR = 0.84; 95% CI, 0.51–1.40, respectively). The RR for exposure during childhood was slightly higher (RR = 1.24; 95% CI, 0.84–1.85) but still not significant.

Reynolds and colleagues (2009) reported on passive smoking and risk of breast cancer using data from the WAVE-II survey (1997) of the California Teachers Study. This analysis was based on 1,754 women with incident invasive breast cancer among a cohort of 57,523 women who were lifetime nonsmokers and followed over 10 years. This report updates one published in 2004 that was based on data from the WAVE-I survey (1995) for 1,174 cases among 77,708 lifetime nonsmokers followed over 4 years (Reynolds et al. 2004b). The WAVE-II survey included more extensive questions on frequency, duration, source, and intensity, and there was a large loss to follow-up from WAVE-I to WAVE-II. The RR for breast cancer with ever-lifetime exposure in the WAVE-II survey was 1.10 (95% CI, 0.94–1.30), adjusting for age, race, and other relevant covariates (Reynolds et al. 2009). The RRs were 1.06 (95% CI, 0.94–1.19) and 1.04 (95% CI, 0.91–1.19) for any childhood (<20 years of age) and any adulthood (≥20 years of age) exposures, respectively; and 1.04 (95% CI, 0.92–1.16) and 1.02 (95% CI, 0.93–1.13) for any home and any work exposures, respectively. Exposure before first pregnancy was also associated with a nonsignificant increased risk

(RR = 1.17, 95% CI, 0.96–1.41) in a fully adjusted analysis. There were trends toward increasing risk with duration and intensity of exposure that reached statistical significance only in the highest category of this combined variable (>42 intensity-years)⁴ in postmenopausal women (RR = 1.25; 95% CI, 1.01–1.56). In this study, the unexposed reference group constituted only 14% of the women in the cohort. The measure of exposure intensity was highly qualitative (self-report of “a little smoky,” “fairly smoky,” and “very smoky”).

Xue and colleagues (2011) reported updated analyses for the NHS-I on active and passive smoking and risk of breast cancer. Their data included 2,890 incident breast cancer cases among 36,017 nonsmoking women followed from 1982–2006. No significant associations were found for any of the following categories of passive exposure: both parents (RR = 0.90; 95% CI, 0.79–1.03), regular at work (RR = 0.87; 95% CI, 0.78–0.98), regular at home (RR = 1.02; 95% CI, 0.90–1.14), and living with a smoker for 40 or more years (RR = 0.99; 95% CI, 0.74–1.32). Indices that combined information on place (home or work) and duration (<20 vs. ≥20 years) of exposure were not significantly associated with risk. All estimates were adjusted for age and multiple relevant covariates but were not stratified by menopausal status.

Also as shown in Table 6.22S, Luo and colleagues (2011b) reported results for passive smoking and incident breast cancer from the Women’s Health Initiative. There were a total of 1,692 incident cases among 41,022 postmenopausal women, who had never smoked, followed over an average of 10.3 years. There were no significant associations between passive exposure during childhood, adulthood at home or at work, or any combination thereof, and risk of breast cancer. The only significant association was for the highest combined category of exposure duration (childhood ≥10 years plus adult at home ≥20 years plus adult at work ≥10 years: RR = 1.32; 95% CI, 1.04–1.67), but the trend across the duration categories for increased risk with greater exposure was not significant ($p = 0.10$). This is one of the only studies to examine exposure to passive smoking in relation to breast cancer by ER/PR status, but no significant associations were found. All estimates were adjusted for age at enrollment and multiple relevant covariates.

Finally, Chuang and colleagues (2011) reported the RR for childhood exposure from parental smoking (RR = 0.98; 95% CI, 0.91–1.06) based on data from 6 of the 23

⁴To predict risk of breast cancer for two age groups (<20 years of age and ≥20 years of age), Reynolds and colleagues (2009) combined two metrics (years of exposure and intensity) into a common metric (intensity-years) that included both intensity (smokiness) and duration (years) of exposure.

centers participating in the EPIC; these centers were in France, Italy, The Netherlands, Sweden, Denmark, and Norway. There were 3,187 breast cancer cases among 92,956 premenopausal and postmenopausal women, 25–70 years of age, who reported themselves to be never smokers at recruitment (1992–1998); the mean age at recruitment was 50 years. Follow-up was over an average of 9–10 years. Significant associations were not found for the two frequency categories of exposure in childhood: few times during a week (RR = 0.98; 95% CI, 0.88–1.10) and daily (RR = 1.06; 95% CI, 0.95–1.19). All estimates were adjusted for age at menarche, ever use of oral contraceptives, parity, menopausal status, education, alcohol use, BMI, physical activity, vegetable intake, fruit intake, non-alcoholic energy intake, and adulthood passive smoking.

Several issues should be considered when comparing and combining the results of these seven studies. First, the categories of exposure were generally broad, particularly in the Norwegian-Swedish cohort (Gram et al. 2005). Second, with the exception of the studies by Pirie and colleagues (2008) and Reynolds and colleagues (2009), analyses were not stratified by menopausal status, use of alcohol, or breast cancer phenotype, although most studies adjusted for these potential confounders. The Norwegian-Swedish Cohort (Gram et al. 2005) consisted mostly of premenopausal women at baseline and the Women's Health Initiative cohort (Luo et al. 2011b) was comprised entirely of postmenopausal women; whereas the Million Women Study (Pirie et al. 2008), Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Lin et al. 2008), California Teachers Study (Reynolds et al. 2009), EPIC (Chuang et al. 2011), and NHS-I (Xue et al. 2011) cohorts included both premenopausal and postmenopausal women. This is important because a previous cohort study by Hanaoka and colleagues (2005) (Table 6.14S) reported markedly different risks for premenopausal (RR = 2.6; 95% CI, 1.3–5.2) and postmenopausal women (RR = 0.7; 95% CI, 0.4–1.0). This difference in risk by menopausal status was also found in the meta-analysis of cohort and case-control studies included in the 2006 Surgeon General's report (USDHHS 2006). Pirie and colleagues (2008) stratified estimates by menopausal status but included few premenopausal women ($n = 60$), and thus the resulting estimate, although significant, was both inverse and imprecise (RR = 0.54; 95% CI, 0.30–0.99). In contrast, the analysis by Reynolds and colleagues (2009) suggests that risk may be increased in postmenopausal rather than premenopausal women. Xue and colleagues (2011), who also stratified by menopausal status, did not provide results that could be used for comparison. Thus, considerable inconsistency remains with regard to the effects of passive smoking exposure by menopausal status.

Third, these cohort studies differ markedly in rates of breast cancer incidence and exposure to passive smoking. In the Japanese cohort study (Lin et al. 2008), which included both in situ and invasive cases, participants had a very low incidence of breast cancer (approximately 58/100,000) compared with the other cohorts (Norwegian-Swedish, approximately 114/100,000; Million Women, approximately 315/100,000; and Women's Health Initiative, approximately 428/100,000). While the difference across these studies for incidence of breast cancer partly reflects the age composition of the respective cohorts, geographic and ethnic/racial differences must be considered also.

Fourth, methods for exposure assessment varied from study to study. For example, the reported prevalence of lifetime (childhood and adulthood) exposure to second-hand smoke varied markedly, from approximately 24% in the Norwegian-Swedish cohort to greater than 90% in the Women's Health Initiative cohort study. As noted in the 2006 Surgeon General's report, these cohort studies lacked updated data about exposure to passive smoking, which can result in some misclassification, especially during long-term followup periods of marked secular change in smoking habits. Xue and colleagues (2011) acknowledged this limitation in the NHS and pointed out that the result would be to attenuate estimates toward the null value because any exposure misclassification may be safely assumed to be nondifferential in a cohort study design. The most recent reports (Reynolds et al. 2009; Luo et al. 2011b; Xue et al. 2011) used novel indices of exposure that combined available information for duration, place, timing, and intensity. The analyses of Reynolds and colleagues (2009) and Luo and colleagues (2011b) suggest increased risk at only the very highest levels of these indices, while the results of Xue and colleagues are essentially null. The analysis of Pirie and colleagues (2008) is unique in restricting the data to women who reported living with a partner. This could be important because women who live alone cannot be passively exposed routinely in the home, a major venue of adult passive exposure. Theoretically, the restriction imposed by Pirie and colleagues (2008) could produce bias because women not living with a partner are likely to differ with respect to multiple risk factors for breast cancer, especially those related to reproductive history.

Case-Control Studies

The 2006 Surgeon General's report evaluated 14 case-control studies on the association between passive smoking and risk for breast cancer. Since then, 10 different case-control studies have been conducted, resulting in 11 published reports (Table 6.23S). Two reports (Metsola

et al. 2005; Sillanpaa et al. 2005a) were based on the same study population; the latter report included adjustment for potential confounders.

North American Studies

Three large case-control studies were conducted in North America (Mechanic et al. 2006; Slattery et al. 2008; Young et al. 2009). In a combined sample of the Ontario Women's Health Study and the Ontario Women's Diet and Health Study (2,751 nonsmoking cases and 3,097 nonsmoking controls), Young and colleagues (2009) reported results on the association between exposure to passive smoking and risk for breast cancer. Exposure to passive smoking was self-reported and defined as exposure less than 2 hours per day during childhood and exposure of at least 2 hours per day for workplace and nonworkplace environments (adult exposure) during the 2 years before the study interview. The study reported an overall OR of 0.97 (95% CI, 0.88–1.08) for exposure to passive smoking compared with a no active/no passive exposure reference group. This estimate was adjusted only for age because the change to the risk estimate was less than 10% when the other potential confounders were included. Stratified analyses by timing of exposure (childhood vs. adulthood), menopausal status, or other relevant variables were not provided.

In the Carolina Breast Cancer Study, which included both African American and White women, Mechanic and colleagues (2006) evaluated the association between exposure to passive smoking and risk for breast cancer among 1,211 nonsmoking cases and 1,087 nonsmoking controls. Passive smoking was broadly defined as living with a smoker after 18 years of age. After adjusting for age, age at menarche, age at first full-term pregnancy, parity, family history, and use of alcohol, the study found an increased risk for breast cancer among African American women (OR = 1.40; 95% CI, 1.00–1.90) but not among White women (OR = 1.00; 95% CI, 0.80–1.20) compared with a no active/no passive exposure reference group. Results were not stratified by menopausal status. For African Americans, risk for breast cancer associated with exposure to passive smoking appeared to increase with the number of at-risk genotypes, which consisted of SNPs in DNA repair genes.

In the 4-Corners Breast Cancer Study, Slattery and colleagues (2008) examined the association between exposure to passive smoking and risk for breast cancer among 1,347 nonsmoking cases and 1,442 nonsmoking controls. Data on exposure to passive smoking was self-reported and captured as the number of exposure hours per week, both in and out of the house, during a reference period of 1 year before cancer diagnosis or study interview and 15, 30, and

50 years of age. Analyses were stratified by menopausal status and Hispanic/non-Hispanic White ethnicity. ORs were adjusted for age, study site, BMI, use of aspirin or NSAIDs, parity, use of alcohol, physical activity, and recent use of estrogen. The study found a significant increased risk only in premenopausal Hispanic women reporting more than 10 hours of exposure to passive smoking per week during the reference period compared with a no active/no passive reference group (OR = 2.3; 95% CI, 1.2–4.5). However, there was an inverse association, albeit nonsignificant, between fewer hours of exposure to passive smoking in this subgroup and risk. In this same subgroup, a significant interaction with a SNP in the *IL6* gene also was detected (see “Secondhand Smoke Exposure and Genotype”). The estimates for postmenopausal women were essentially null, and those for non-Hispanic White premenopausal women were increased by about 20%. The overall lifetime summary estimate (OR) calculated for this report was 1.06 (95% CI, 0.88–1.28).

Taken together, these large case-control studies do not provide evidence that exposure to secondhand smoke is a risk factor for breast cancer. However, the assessment of exposure to passive smoking was relatively crude in two studies that did not stratify results for potential effect modifiers—timing of exposure or menopausal status. Three additional case-control studies conducted in North America collected more extensive exposure data, but the results are difficult to interpret because of small samples (Alberg et al. 2004; Rollison et al. 2008; Ahern et al. 2009). In a case-control study in Massachusetts (242 nonsmoking cases, 195 nonsmoking controls), Ahern and colleagues (2009) collected information about exposure to passive smoking according to stage of life (childhood, adulthood), parental source during childhood (father, mother), and location (home, workplace). Overall, the results were null; only two significantly increased risks were reported: one for exposure during childhood from a mother who smoked (OR = 1.9; 95% CI, 1.1–3.3), and the other for postmenopausal women exposed during childhood (OR = 1.8; 95% CI, 1.0–3.3). In a small case-control study in Delaware (124 nonsmoking cases, 116 nonsmoking controls), Rollison and colleagues (2008) collected extensive data on exposure to passive smoking at home during childhood and adulthood and at the workplace in adulthood. Data included estimates of the number of smokers in the household, number of hours of exposure per day, and intensity of exposure (packs of cigarettes smoked per day). Compared with a no active/no passive exposure reference group, the study did not find any significant increased ORs across any exposure category, but statistical power was limited by the small sample. In another small case-control study (115 cases and 115 controls matched for age, race, and

menopausal status), Alberg and colleagues (2004) assessed the association between passive smoking, defined as living with a spouse who smoked, and risk for breast cancer. Data were available for only 62 nonsmoking cases and 66 nonsmoking controls. The OR for breast cancer was 1.2 (95% CI, 0.59–2.4). The study observed a nonsignificant interaction between exposure to passive smoking and the NAT2 phenotype.

European Studies

Five reports based on four case-control studies in Europe have been published since the 2006 Surgeon General's report. Two of these studies were conducted in Poland (Lissowska et al. 2006; Kruk 2007), one in Finland (Metsola et al. 2005; Sillanpaa et al. 2005a), and one in England (Roddam et al. 2007).

The largest European study was conducted by Lissowska and colleagues (2006) and had 1,034 nonsmoking cases and 1,162 nonsmoking controls. Passive smoking was self-reported and defined as adult exposure at home or in the workplace for at least 1 hour per day for at least 1 year. In a comparison with a no active/no passive exposure reference group, this study did not find significant associations between risk for breast cancer and exposure to passive smoking at home, at the workplace, at *both* home and the workplace, or for either the home or workplace. After adjusting for relevant covariates, the OR was 1.10 (95% CI, 0.84–1.45) for either the home or workplace. The initial analyses did not stratify risk by stage of life (childhood, adulthood), age group, or menopausal status. A subsequent reanalysis, however, which was published as a response to a letter to the editor by Johnson (2007), reported results that were stratified by age group and menopausal status (Lissowska et al. 2007). Premenopausal women (Table 6.23S) exhibited increasing ORs for breast cancer by hours of exposure to secondhand smoke per day-years⁵: less than 100, 1.36 (95% CI, 0.67–2.73); 101–200, 1.52 (95% CI, 0.73–3.13); and more than 200, 2.02 (95% CI, 0.94–4.36) (p trend = 0.08). The indicator of hours per day-years was calculated as the product of hours of exposure per day and duration of exposure. Of note, the study did not find similar trends for either of the two age groups (younger than 45 years of age and 45–55 years of age) that included all premenopausal women.

Kruk (2007) reported results from an independent case-control study in Poland (445 nonsmoking cases,

730 nonsmoking controls). For this study, Kruk defined exposure to passive smoking as living with a spouse who smoked and defined dose as number of cigarettes smoked per day. In contrast to Lissowska and colleagues (2007), Kruk (2007) reported significant ORs for premenopausal women (2.86; 95% CI, 1.65–4.97) and postmenopausal women (2.57; 95% CI, 1.73–3.80). These estimates, however, were adjusted only for age among premenopausal women and age and breastfeeding among postmenopausal women, and smokers were mixed with nonsmokers in the reference group. Among case-control studies, this study provides some of the highest ORs for active and passive smoking.

Roddam and colleagues (2007) conducted a study in England of women, 36–45 years of age, who were mostly premenopausal. Exposure to passive smoking at home was defined as living at least 1 year with a partner who smoked, and dose was defined as the number of years of exposure and estimated number of cigarettes smoked per day. After adjusting for relevant covariates, exposure to secondhand smoke was not significantly associated with risk for breast cancer (OR = 0.89; 95% CI, 0.64–1.25) among 297 nonsmoking cases and 310 nonsmoking controls when no passive/no active exposure was the reference group. Estimates were stratified on menopausal status, but the number of perimenopausal/postmenopausal women (n = 23) was too small to provide a meaningful result.

Metsola and colleagues (2005) and Sillanpaa and colleagues (2005a) published results on the same case-control study in Finland. Both focused on the modification of active smoking by selected SNPs in DNA repair and NAT2 genes, but both reports provided only a cursory description of how exposure to passive smoking was defined in terms of years at home and the workplace. The two reports provided ORs for the association between exposure to passive smoking and risk for breast cancer (153 nonsmoking cases, 169 nonsmoking controls), but only the estimate from Sillanpaa and colleagues (2005a) was adjusted for multiple covariates; this estimate was not significant (OR = 0.85; 95% CI, 0.62–1.16). Stratification on the NAT2 phenotype suggested that risk for breast cancer was increased in women with the slow phenotype who were passively exposed to tobacco smoke (OR = 1.22; 95% CI, 0.75–1.98).

⁵Day-years: the sum of hours per day exposed to secondhand smoke multiplied by the number of years of all episodes of secondhand smoke exposure, whether at home, at work, or during leisure time.

Asian Studies

Findings from case-control studies carried out in Asia on secondhand smoke have not been published since 2005. However, the 2006 Surgeon General's report did not include the hospital-based, cross-sectional study by Hirose and colleagues (1995) that was conducted in Japan. Using a large administrative database that had data for cigarette smoking and exposure to secondhand smoke, the study identified 1,052 breast cancer cases with survey data and 23,163 controls without a cancer diagnosis. The analysis for passive smoking was limited to women who reported being nonsmokers (560 cases and 11,276 controls). The prevalence of smoking in the control group (14%) was similar to that in the general population of women in Japan (13%). Passive smoking among women who were nonsmokers was defined on the basis of whether the husband smoked and the number of cigarettes he smoked per day (either 0–19 or ≥ 20). Among premenopausal women, risk for breast cancer increased as the number of cigarettes smoked per day by the husband rose: 0–19 (RR = 0.81; 95% CI, 0.57–1.15) and 20 or more (RR = 1.30; 95% CI, 1.02–1.65). There was no similar dose-response relationship in postmenopausal women: 0–19 (RR = 1.55; 95% CI, 1.10–2.17) and 20 or more (RR = 1.28; 95% CI, 0.92–1.77). The study had several limitations: it was clinic based and may have included prevalent as well as incident cases, data were missing on passive smoking for 38% of nonsmoking women, and risk estimates were adjusted only for age and year of first visit to a clinic.

Meta-Analysis of Breast Cancer Risk Associated with Measures of Secondhand Smoke

A total of 19 new published reports (7 cohort, 12 case-control) were reviewed together with the 20 reports (5 cohort, 15 case-control) that were previously abstracted and analyzed for the 2006 Surgeon General's report. Three of these update previous reports from the same studies and one overlaps with a current report (Table 6.24S). RR and OR estimates were based on either single estimates or were pooled across exposure strata and classified similarly to the eight categories reported in the 2006 Surgeon General's report. The same statistical procedures used in the meta-analyses for active cigarette smoking were used for the analyses of exposure to secondhand smoke. Sensitivity analyses considered study design, sample size, and magnitude of exposure effect.

Table 6.24S provides a listing of the 39 reports for 34 studies, of which 9 overlap with results on the same study population. Of these, 7 are included in the meta-analyses because they are either the most recent or complete reports from their study. In the case of 1 cohort study (California Teachers Study) and 1 case-control study (Carolina Breast Cancer Study), the best exposure estimates for specific categories were selected for inclusion in the meta-analyses: California Teachers Study (Reynolds et al. 2004b, 2009) and Carolina Breast Cancer Study (Millikan et al. 1998; Marcus et al. 2000; Mechanic et al. 2006). A total of 34 separate reports were included in the broadest category of exposure for the meta-analyses: *Most comprehensive*. RR and OR estimates were pooled across exposure levels to fit into one of the meta-analysis categories when necessary.

Measures of Exposure to Secondhand Smoke

This meta-analysis used eight categories of measures of exposure to secondhand smoke. These categories are not mutually exclusive, and assignments are presented in Table 6.24S.

1. **Spouse/partner:** This category was based on exposure during adulthood from a spouse or partner who was a smoker.
2. **Adult—home:** This category was based on exposure during adulthood from any smoker in the home. The category *Spouse/partner* is a subset of *Adult—home* because the location of exposure was assumed to be in the home.
3. **Adult—workplace:** Based on exposure during adulthood from smokers at the workplace, an estimate from this category could be used for any adult. However, most studies with a measure for exposure at the workplace had a measure for exposure at home that took precedence.
4. **Childhood:** This category was based on exposure during childhood to any smoker in the home. Among the 15 studies that provided a childhood estimate, the age definition of childhood varied. Sixteen, 18, or 21 years of age defined the end of childhood exposure in 7 studies (Smith et al. 1994; Marcus et al. 2000; Gammon et al. 2004a; Bonner et al. 2005; Rollison et al. 2008; Chuang et al. 2011; Luo et al. 2011b), and the remaining studies did not define a specific cutoff for age (Johnson et al. 2000;

Liu et al. 2000; Kropp and Chang-Claude 2002; Lin et al. 2008; Pirie et al. 2008; Ahern et al. 2009; Reynolds et al. 2009; Xue et al. 2011).

5. **Adulthood and childhood (or lifelong):** This category was based on lifelong exposure during childhood and adulthood from any individual in any setting. Only seven studies defined exposure in this manner (Smith et al. 1994; Johnson et al. 2000; Kropp and Chang-Claude 2002; Reynolds et al. 2004b; Pirie et al. 2008; Ahern et al. 2009; Luo et al. 2011b).
6. **Adult—any source:** This category was based on the broadest, most inclusive measure available for exposure during adulthood from any source in the following priority: a general estimate for all sources of exposure if available, a comprehensive home exposure, spouse/partner exposure, and workplace exposure. Twenty-six non-overlapping reports included measures that were coded for this category based on a number of descriptive measures, including a general report for overall and nonspecific exposure to passive smoke as an adult (Johnson et al. 2000; Kropp and Chang-Claude 2002; Ahern et al. 2009); exposure specifically noted as from a spouse or partner (Sandler et al. 1985a; Hirose et al. 1995; Morabia et al. 1996; Jee et al. 1999; Nishino et al. 2001; Alberg et al. 2004; Gammon et al. 2004a; Kruk 2007; Roddam et al. 2007; Pirie et al. 2008); cohabitants in general (Smith et al. 1994; Delfino et al. 2000; Liu et al. 2000; Mechanic et al. 2006; Lin et al. 2008; Reynolds et al. 2009; Xue et al. 2011); coworkers (Bonner et al. 2005; Hanaoka et al. 2005); or a combination of cohabitants and coworkers (Shrubsole et al. 2004; Sillanpaa et al. 2005a; Lissowska et al. 2006; Luo et al. 2011b).
7. **Ever in lifetime:** Based on a report of exposure to passive smoke during either childhood or adulthood in studies that assessed exposure across the lifetime, this category can include, for example, an estimate based on exposure during adulthood if exposure during childhood was also assessed and included in the risk estimate. The category *Adulthood and childhood* is a subset of *Ever in lifetime*. Twenty nonoverlapping reports had measures that were coded for this category based on definitions that ranged from very general to specific. One study estimate was based on exposure during childhood and adulthood (Ahern et al. 2009); 5 were based on lifetime exposure in the

home (Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Bonner et al. 2005; Slattery et al. 2008); 4 were based on any exposure from a spouse or a parent during the lifetime (Gammon et al. 2004a; Gram et al. 2005; Pirie et al. 2008; Chuang et al. 2011); 1 was based on having lived with a smoker or been exposed to a smoker outside of the home (Hanaoka et al. 2005); 5 were based on having lived with a smoker or been exposed at the workplace (Smith et al. 1994; Morabia et al. 1996; Johnson et al. 2000; Kropp and Chang-Claude 2002; Rollison et al. 2008); and 4 were based on any exposure during childhood or adulthood without information about location or source of exposure (Reynolds et al. 2009; Young et al. 2009; Xue et al. 2011). The broadest measure for *Ever in lifetime* was selected in those studies that reported more than one category of exposure during childhood and adulthood. The home was the most frequently defined location for exposure; outside the home and/or at the workplace were identified less frequently. Studies varied widely in specificity and rigor of the definition of lifetime exposure.

8. **Most comprehensive:** This category was based on the broadest, most inclusive estimate of exposure available from each study. In the meta-analysis, this was always either *Adult—any source* or *Ever in lifetime*, with preference for the latter when both estimates were reported. A careful evaluation was made of the independent contributions of each category to the summary estimate for the *Most comprehensive* (see *Comparison of Adult—Any Source with Ever in Lifetime for Most Comprehensive*).

This meta-analysis applied some changes to the studies reviewed in the 2006 Surgeon General's report, including the exclusion of two mortality studies (Hirayama 1984; Wartenberg et al. 2000), the inclusion of a study conducted in China and published prior to 2005 (Hirose et al. 1995), and changes to several estimates for five studies (Smith et al. 1994; Millikan et al. 1998; Jee et al. 1999; Nishino et al. 2001; Gammon et al. 2004a). These changes are detailed in the notes for Table 6.24S. Risk estimates were abstracted for each study, classified into the eight categories described previously, and tabulated together with information on adjusted covariates, including reproductive risk factors, alcohol use, BMI, family history, and menopausal status. The most fully adjusted estimates were selected when available, and a random effects model was used to pool estimates across strata (e.g., race/ethnicity, menopausal status, or dose levels) when necessary.

Adjustment for Selected Covariates

The majority of studies that evaluated exposure to passive smoke adjusted for covariates, most often referencing those that were related to reproduction or estrogen, but also family history, use of alcohol, and BMI. Of the 34 separate studies, only 4 did not adjust for any covariate or adjusted for age only (Sandler et al. 1985a; Jee et al. 1999; Alberg et al. 2004; Metsola et al. 2005).

Most Comprehensive Measures of Passive Smoking

Among the 34 studies included in the meta-analysis of passive smoking and risk for breast cancer, only 7 did not report estimates for measures of active smoking (Jee et al. 1999; Liu et al. 2000; Nishino et al. 2001; Bonner et al. 2005; Pirie et al. 2008; Reynolds et al. 2009; Chuang et al. 2011). Eight of the 34 studies were based on Asian populations (Hirose et al. 1995; Jee et al. 1999; Zhao et al. 1999; Liu et al. 2000; Nishino et al. 2001; Shrubsole et al. 2004; Hanaoka et al. 2005; Lin et al. 2008), and 8 studies included data on the interaction between genotype and smoking for risk for breast cancer (Delfino et al. 2000; Alberg et al. 2004; Gammon et al. 2004a; Metsola et al. 2005; Sillanpaa et al. 2005a; Lissowska et al. 2006; Mechanic et al. 2006; Slattery et al. 2008). Figure 6.40 presents the 34 studies (10 cohort and 24 case-control) that were based on the *Most comprehensive* category, which was derived from either the *Adult—any source* ($n = 14$) or *Ever in lifetime* ($n = 20$) measures. Meta-analysis provided an overall summary RR of 1.14 (95% CI, 1.06–1.23), but with significant heterogeneity ($p_h < 0.001$) (Table 6.25S). The funnel plot in Figure 6.41 shows evidence of significant skewness, suggesting the presence of publication bias, as indicated by the lack of smaller negative studies. This was further confirmed (Figure 6.40) by Begg's rank correlation test ($z = 2.30$, $p = 0.02$) and the Egger test (bias = 1.41, $p = 0.007$). Stratification by study design (Table 6.25S) revealed that the heterogeneity resulted mainly from the variation among the 24 case-control studies (RR = 1.27; 95% CI, 1.11–1.44; $p_h < 0.000$), although significant heterogeneity was also found for the 10 cohort studies (RR = 1.02; 95% CI, 0.95–1.10; $p_h = 0.038$).

The funnel plot in Figure 6.41 also indicates the presence of some studies with extreme outlier estimates (i.e., those that fall well outside the boundaries of the funnel) (Smith et al. 1994; Morabia et al. 1996; Lash and Ashengrau 1999; Zhao et al. 1999; Kruk 2007). Because extreme estimates can strongly affect a summary estimate, these outlier studies were inspected more closely for potential problems with study design. The case-control

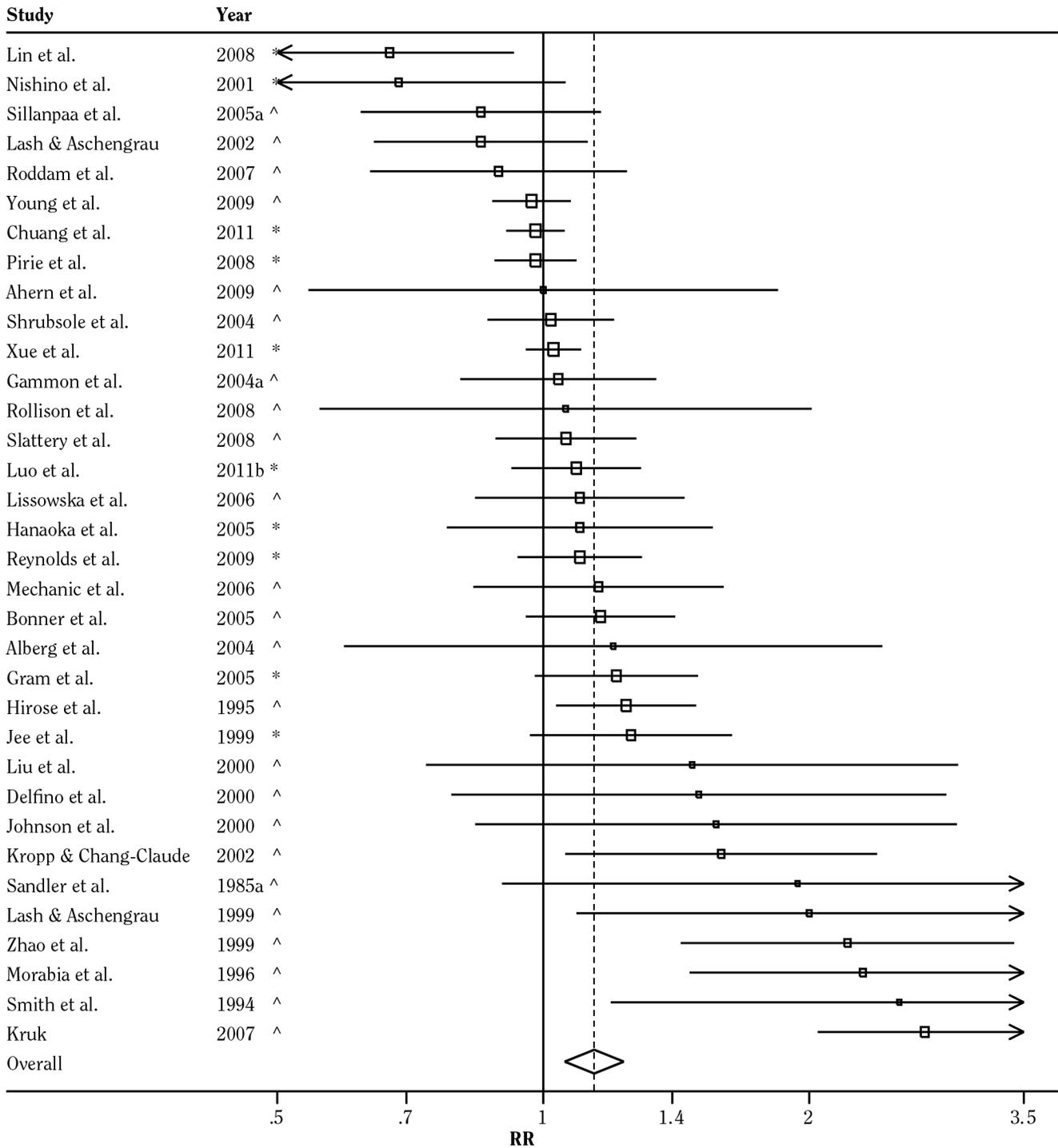
studies by Kruk (2007) and Zhao and colleagues (1999) appeared to include smokers along with nonsmokers in the analysis of exposure to passive smoke. Furthermore, the number of cases and controls reported in the tables in both of these studies could not be reconciled with totals provided in the text or in other tables. Excluding these two studies (Table 6.25S) attenuated the overall risk estimate (RR = 1.08; 95% CI, 1.01–1.14; $p_h = 0.001$; $n = 32$) and the risk estimate for the case-control studies (RR = 1.14; 95% CI, 1.04–1.26; $p_h = 0.003$; $n = 22$).

The extreme estimate from Smith and colleagues (1994) was based on a very small subset of cases and controls ($n = 193$) that represented only 27% of the nonsmokers ($n = 703$) in the full study. Other studies were also based on a small number of cases. For example, estimates reported by Morabia and colleagues (1996) were based on only 126 cases (620 controls), and the results from the cohort study by Lin and colleagues (2008) were based on only 140 incident cases. However, although small studies are statistically more likely to produce extreme estimates, these studies adjusted for appropriate covariates and did not have other limitations to their respective designs.

Limitations in study design were detected in three other studies that did not provide extreme estimates. Two studies included an unknown percentage of deceased persons for whom information was collected from proxies and did not adjust for menopausal status (Lash and Ashengrau 1999, 2002), and one study included both incident and prevalent cases based on medical records and did not adjust for covariates relevant to breast cancer (including menopausal status) other than age (Jee et al. 1999). Excluding these three studies plus Kruk (2007) and Zhao and colleagues (1999) (Table 6.25S) did not meaningfully alter the overall summary estimate (RR = 1.07; 95% CI, 1.01–1.13; $p_h = 0.002$; Begg $z = 2.21$; $p = 0.03$; Egger bias = 0.98; $p = 0.02$, $n = 29$).

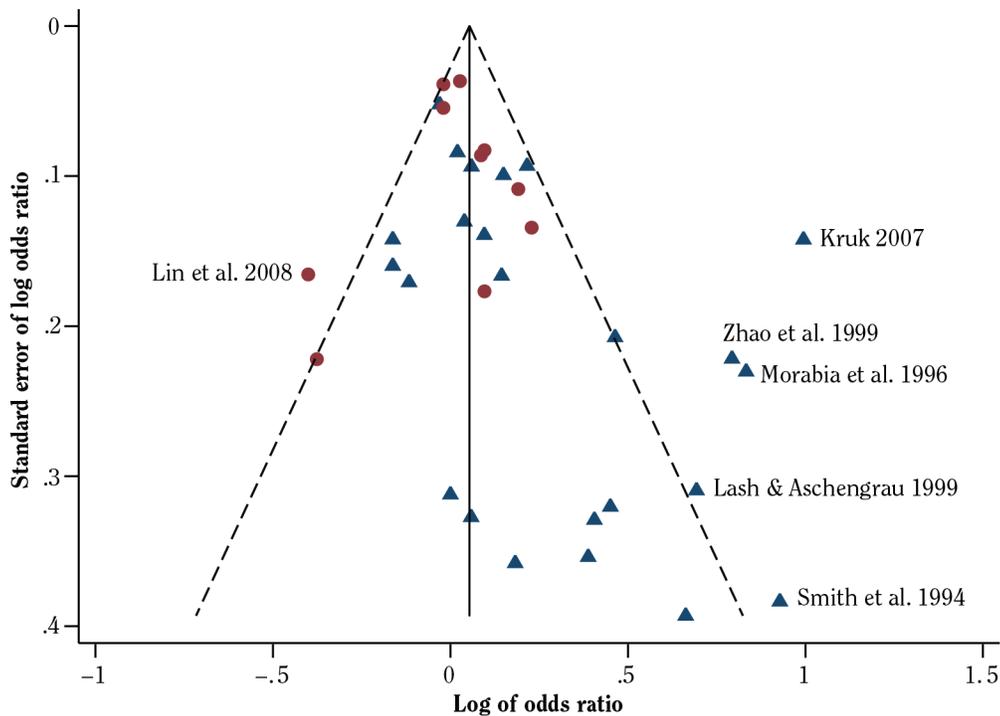
Because the funnel plot in Figure 6.41 indicated publication bias stemming from small studies, 5 more studies with fewer than 100 cases were excluded (Sandler et al. 1985a; Smith et al. 1994; Delfino et al. 2000; Nishino et al. 2001; Alberg et al. 2004) in addition to the 5 with design limitations (Jee et al. 1999; Lash and Ashengrau 1999, 2002; Zhao et al. 1999; Kruk 2007). The summary estimate (RR) then became 1.06 (95% CI, 1.00–1.12; $n = 24$). Although significant heterogeneity remained ($p_h = 0.010$), excluding the 10 studies reduced publication bias, as expected (Begg $z = 1.79$; $p = 0.07$; Egger bias = 0.95; $p = 0.05$). However, the estimate by Morabia and colleagues (1996) remained an extreme outlier. Excluding this study resulted in a summary estimate (RR) of 1.04 (95% CI, 0.99–1.09; $p_h = 0.131$; $n = 23$). Figure 6.42

Figure 6.40 Forest plot showing the association between the most comprehensive measure of exposure to second-hand smoke and risk for breast cancer, based on the subset of cohort and case-control studies published before 2012 (n = 34)



Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.14 (95% CI, 1.06–1.23); Begg z = 2.30, p = 0.02; Egger bias = 1.41, p = 0.007. See Table 6.24S for five overlapping reports that were excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

Figure 6.41 Funnel plot showing estimates in the meta-analysis of the most comprehensive measure of exposure to secondhand smoke with risk for breast cancer, based on the subset of cohort and case-control studies published before 2012 ($n = 34$)



Note: l = cohort study; p = case-control study. Includes the same studies reported in Figure 6.40.

shows the forest plot for the 23 studies that remained after the exclusions. The accompanying funnel plot in Figure 6.43 shows that publication bias (Begg $z = 1.35$; $p = 0.18$; Egger bias = 0.68; $p = 0.12$; see note for Figure 6.42) and the effects of case-control studies with extreme estimates well outside of the 95% CI of the funnel no longer leveraged the RR. The case-control studies that were removed did not appear to have better assessments of exposure than many other studies that were included. While the estimate for the cohort study by Lin and colleagues (2008) is just outside the outer margin of the funnel, it is balanced by the estimate for the case-control study by Kropp and Chang-Claude (2002).

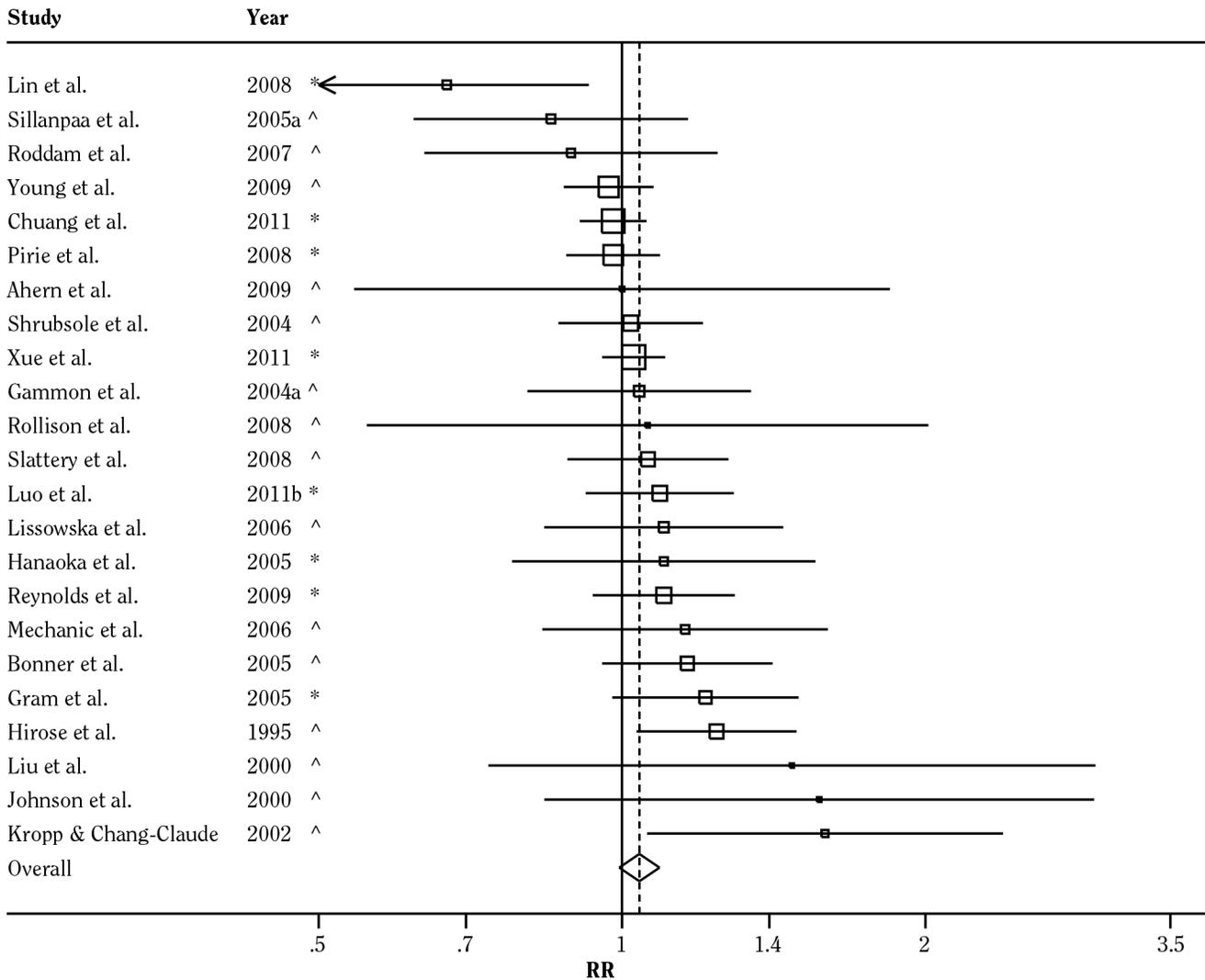
Comparison of Adult—Any Source with Ever in Lifetime for Most Comprehensive

An evaluation was made of whether an additional source of bias in the meta-analysis of the *Most comprehensive* category was due to a mix of the *Ever in lifetime* ($n = 20$) and *Adult—any source* ($n = 14$) measures of exposure (see Table 6.24S for listing of studies). As

described previously, the *Ever in lifetime* category uses a broad definition of passive exposure—that is, it includes studies with estimates based on exposure to passive smoke during childhood and adulthood. In contrast, the *Adult—any source* category provides a measure mainly of current exposure that often includes both source (spouse, partner) and location (home, workplace). The *Most comprehensive* category was based on the *Ever in lifetime* category when both results were available.

The summary RR for all 26 studies with an *Adult—any source* estimate was 1.15 (95% CI, 1.03–1.28; $p_h < 0.001$) (Table 6.25S), and the summary estimate for the subset of 14 studies contributing to the *Most comprehensive* category was nearly identical: RR = 1.15; 95% CI, 0.94–1.39 (data not shown). In contrast, all 20 studies with an estimate for the category *Ever in lifetime* were included in the *Most comprehensive* category. The summary RR for these 20 studies was 1.11 (95% CI, 1.03–1.20; $p_h < 0.001$) (Table 6.25S). There was less indication of publication bias for the 14 studies in the *Adult—any source* exposure category (Begg $z = 0.38$, $p = 0.70$; Egger bias = 0.23, $p = 0.88$)

Figure 6.42 Forest plot showing the association between the most comprehensive measure of secondhand smoke and risk for breast cancer, based on the subset of cohort and case-control studies published before 2012, excluding studies with design or analysis issues (n = 23)



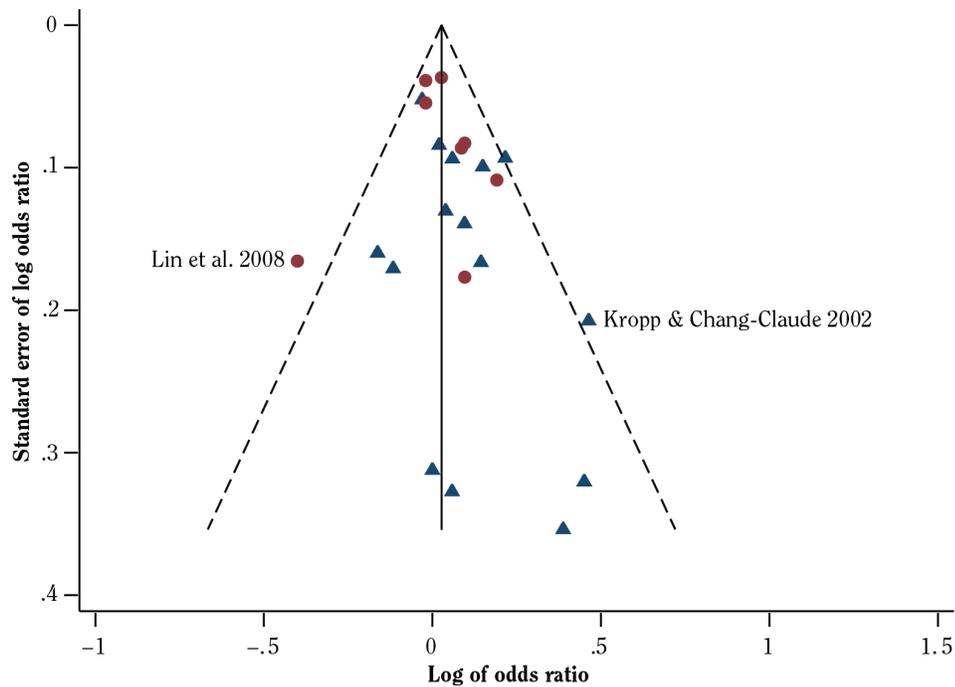
Note: * = cohort study; ^ = case-control study. Meta-analysis RR = 1.04 (95% CI, 0.99–1.09); Begg z = 1.35, p = 0.18; Egger bias = 0.68, p = 0.12. See Table 6.25S (note f) for studies excluded. Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. CI = confidence interval; RR = relative risk.

than for the 20 studies in the *Ever in lifetime* category (Begg z = 2.60, p = 0.009; Egger bias = 1.84, p = 0.001), as shown in funnel plots in Figure 6.44.

When small studies, those with design or analysis issues, and the 1 outlier study (Morabia et al. 1996) were excluded from each of the two categories, the RRs were attenuated similarly. The exclusion of 6 of the 14 *Adult—any source* studies resulted in an RR of 1.01 (95% CI,

0.88–1.17; n = 8) (data not shown). The exclusion of 5 of the 20 *Ever in lifetime* studies resulted in an RR of 1.03 (95% CI, 0.99–1.07; n = 15) (Table 6.25S). Thus, the exclusion of these 11 studies did not produce differential bias between the *Adult—any source* and *Ever in lifetime* categories that were used for the *Most comprehensive* RR. The RR for all studies in the *Adult—any source* and *Ever in lifetime* categories as well as in the reduced analyses after

Figure 6.43 Funnel plot for estimates in the meta-analysis of the most comprehensive measure of exposure to secondhand smoke with risk for breast cancer, based on the subset of cohort and case-control studies published before 2012, excluding studies with design or analysis issues (n = 23)



Note: l = cohort study; p = case-control study. Includes the same studies reported in Figure 6.42.

exclusions were similar. Thus, one of these two categories does not provide a better assessment of exposure than the other, nor is one of the categories a greater source of bias in the meta-analyses than the other.

Comparison of Premenopausal with Postmenopausal for Most Comprehensive

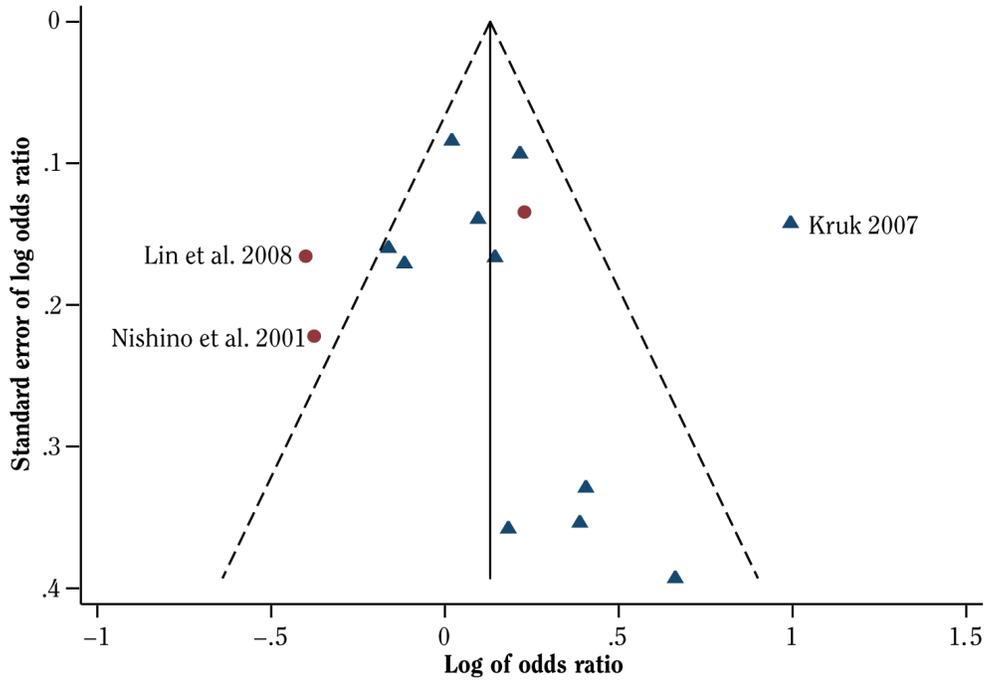
The meta-analysis for the *Most comprehensive* measure of exposure to passive smoke was stratified on menopausal status for all studies with available estimates (Table 6.25S). The summary estimate (RR) for 17 studies with data on exposure among premenopausal women was 1.45 (95% CI, 1.20–1.75; $p_h < 0.001$) (Table 6.25S). The funnel plot in Figure 6.45A displays substantial publication bias associated with an excess of positive estimates from smaller studies with data for premenopausal women (Begg $z = 2.97$, $p = 0.003$; Egger bias = 2.61, $p = 0.001$). Fourteen case-control studies produced a summary estimate of 1.52 (95% CI, 1.23–1.87; $p_h < 0.001$) for premenopausal women, and 3 cohort studies produced a summary estimate for this group of 1.23 (95% CI, 0.69–

2.19; $p_h = 0.027$) (Table 6.25S). In contrast, the summary estimate (RR) for 17 studies with data for postmenopausal women was 1.11 (95% CI, 0.99–1.25; $p_h = 0.001$) (Table 6.25S). Although the estimate for 1 study was an extreme outlier (Kruk 2007), the funnel plot for postmenopausal women in Figure 6.45B does not reveal substantial bias (Begg $z = 0.91$, $p = 0.37$; Egger bias = 0.78, $p = 0.31$). For postmenopausal women, the summary estimate for 13 case-control studies was 1.18 (95% CI, 1.00–1.39; $p_h = 0.004$), and the summary estimate for 4 cohort studies was 1.01 (95% CI, 0.85–1.20; $p_h = 0.035$) (Table 6.25S). According to Figure 6.45A, estimates for studies that reported exposure among premenopausal women were not randomly distributed within the boundaries of the funnel plot; an excess of small studies had positive estimates; and a few studies were extreme outliers, appearing outside the upper level of the pseudo 95% CI. This is less apparent in the funnel plot for studies that reported exposure among postmenopausal women (Figure 6.45B).

Exclusion of the 11 studies with design or analysis limitations, small samples, or extreme estimates had a major impact on all estimates for the *Most comprehen-*

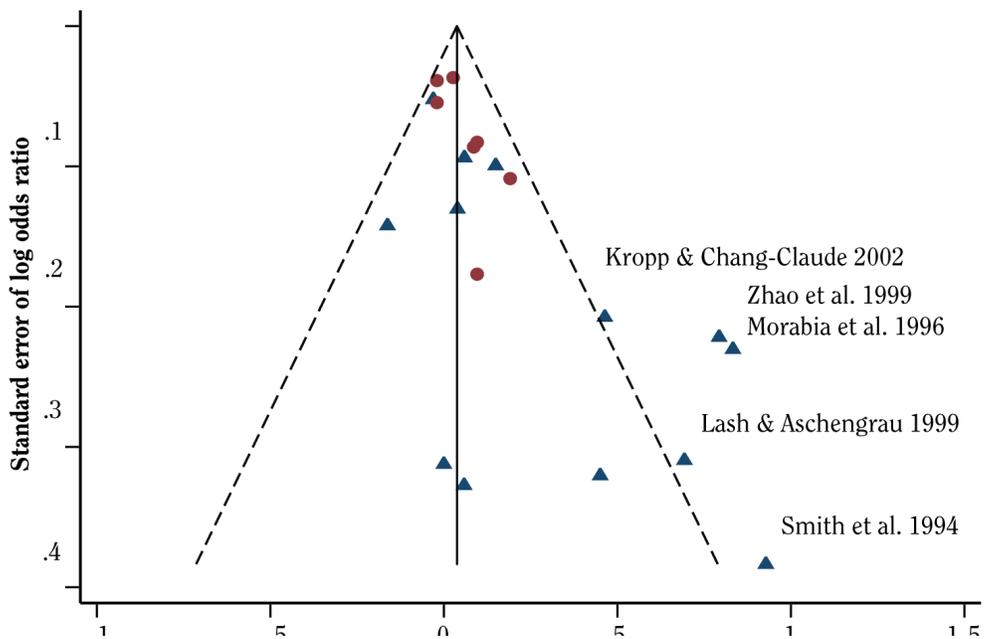
Figure 6.44 Funnel plots for estimates in the meta-analysis of *Adult—any source* (n = 14) and *Ever in lifetime* (n = 20) measures of exposure to secondhand smoke that contributed to the *Most comprehensive exposure* category, based on the subset of cohort and case-control studies published before 2012 (n = 34)

A. Adult—any source



RR = 1.15 (95% CI, 0.94–1.39); Begg z = 0.38, p = 0.070; Egger bias = 0.23, p = 0.88.

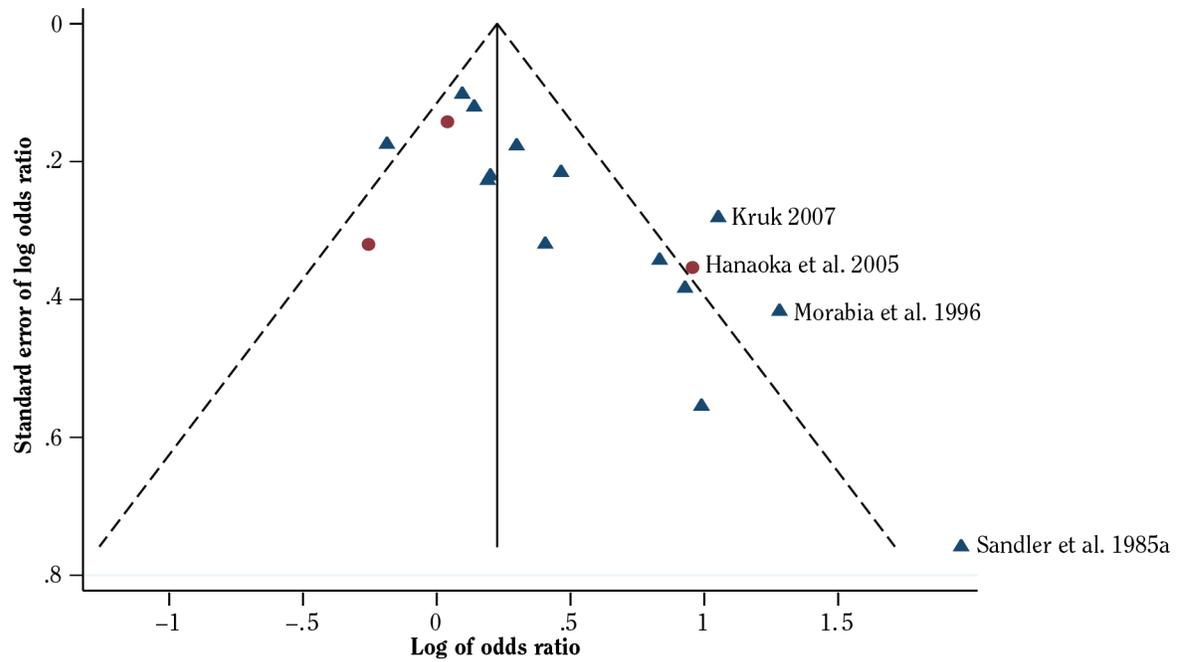
B. Ever in lifetime



Note: l = cohort study; p = case-control study. Comparison of all 34 studies that contributed to the *Most comprehensive* measure of passive exposure to smoke, stratified by exposure category: *Adult—any source* versus *Ever in lifetime* (See Table 6.24S, *Most comprehensive: Adult—any source* versus *Ever in lifetime*) for studies included in each figure.

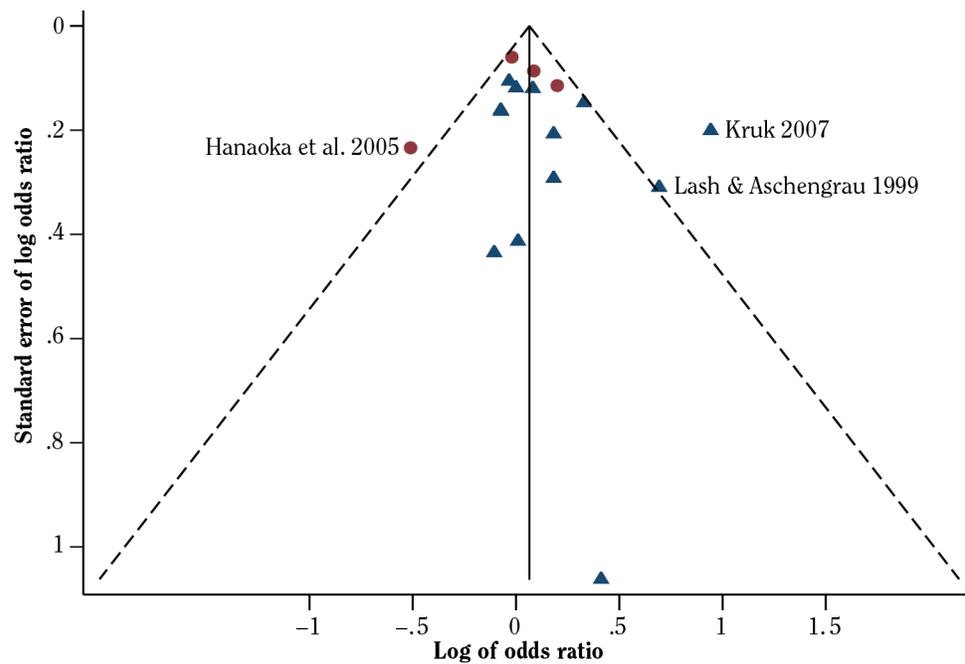
Figure 6.45 Funnel plots showing estimates in the meta-analysis of premenopausal (n = 17) and postmenopausal (n = 17) status for the *Most comprehensive* measure of exposure to secondhand smoke with risk for breast cancer, based on the subset of cohort and case-control studies published before 2012

A. Premenopausal



Meta-analysis RR = 1.45 (95% CI, 1.20–1.75); Begg z = 2.97, p = 0.003; Egger bias = 2.61, p = 0.001.

B. Postmenopausal



Meta-analysis RR = 1.11 (95% CI, 0.99–1.25); Begg z = 0.91, p = 0.37; Egger bias = 0.78, p = 0.31.

Note: l = cohort study; p = case-control study. See Table 6.24S (Premenopausal, Postmenopausal) for studies included in each figure. There were two studies with estimates for only premenopausal women (Smith et al. 1994; Morabia et al. 1996), and two studies with estimates for only postmenopausal women (Lash and Ashengrau 1999; Luo et al. 2011b).

sive exposure category, with the summary estimate for all studies decreasing from 1.14 to 1.04 (Table 6.25S). The summary estimate for premenopausal women decreased from 1.45 to 1.21 (Table 6.25S, Figure 6.46A), and the summary estimate for postmenopausal women decreased from 1.11 to 1.04 (Table 6.25S, Figure 6.46B).

Taken together, these sensitivity and stratified analyses suggest that the meta-analysis of the *Most comprehensive* exposure category, which included both the *Adult—any source* and *Ever in lifetime* definitions of exposure, produced highly heterogeneous results, and that the summary estimate was subject to bias from small case-control studies, some of which had extreme (outlier) estimates (Table 6.25S). The summary result for premenopausal women may have been influenced by smaller case-control studies that reported statistically significant, positive associations. However, among the three cohort studies, the report by Hanaoka and colleagues (2005), with relatively few breast cancer cases, stands out as reporting a significant increased risk for breast cancer in premenopausal women (RR = 2.6; 95% CI, 1.3–5.2) and a reduced risk in postmenopausal women (RR = 0.70; 95% CI, 0.4–1.0). These findings are inconsistent with those from the other two larger and more recent cohort studies that reported no significantly increased or decreased risk in either premenopausal women, RR = 1.04; 95% CI, 0.79–1.38 (Reynolds et al. 2009); or postmenopausal women, RR = 1.22; 95% CI, 0.97–1.52 (Reynolds et al. 2009) and RR = 1.09; 95% CI, 0.92–1.29 (Luo et al. 2011b).

Other Categories of Passive Exposure

For comparison with the findings of the 2006 Surgeon General's report, Table 6.26S summarizes the results of the meta-analysis for other exposure categories: childhood, childhood and adulthood, and adulthood (spouse, home, and workplace). Most of the summary estimates are similar to those in the 2006 report, but several changed because of new studies published since 2006 with data for these categories.

There are now 15 studies (5 cohort and 10 case-control) with estimates for passive smoking exposure from the spouse versus 9 in the 2006 Surgeon General's report. The summary RR for these studies is 1.22 (95% CI, 1.05–1.42; $p_h = 0.001$), similar to the 2006 estimate of 1.17 (95% CI, 0.96–1.44; $p_h = 0.002$). However, when 7 studies with design or analysis issues are excluded, the RR drops to 1.05 (95% CI, 0.97–1.13; $p_h = 0.185$). The previous Surgeon General's report provided a summary RR of 1.01 (95% CI, 0.85–1.19; $p_h = 0.006$) for 8 studies reporting passive exposure at home. There are now 20 studies for home exposure (7 cohort and 13 case-control), for which the summary RR is 1.16 (95% CI, 1.02–1.31; $p_h =$

0.001). When 8 studies with design or analysis issues are excluded, the estimate drops considerably, in this case to 1.02 (95% CI, 0.94–1.11; $p_h = 0.061$). The new summary estimates for exposure in the workplace (RR = 1.03; 95% CI, 0.92–1.15) and during childhood (RR = 1.01; 95% CI, 0.95–1.07) are quite close to the estimates in the 2006 Surgeon General's report. For exposure in childhood and adulthood, however, the previous estimate, based on 4 studies, was 1.39 (95% CI, 0.88–2.18; $p_h = 0.021$) compared to 1.09 (95% CI, 0.95–1.24; $p_h = 0.102$) based on a new total of 7 studies.

Results for these exposure categories by menopausal status are considered unstable because they are based on nine or fewer studies. Moreover, only two of the summary RRs are significant: exposure to secondhand smoke at home among premenopausal women ($n = 9$; RR = 1.35; 95% CI, 1.03–1.78; $p_h = 0.003$); and, exposure during childhood among postmenopausal women ($n = 4$; RR = 1.15; 95% CI, 1.03–1.28; $p_h = 0.888$). In general, point estimates tend to be higher in premenopausal than postmenopausal women, but it is difficult to interpret this difference because the CIs are wide and overlapping.

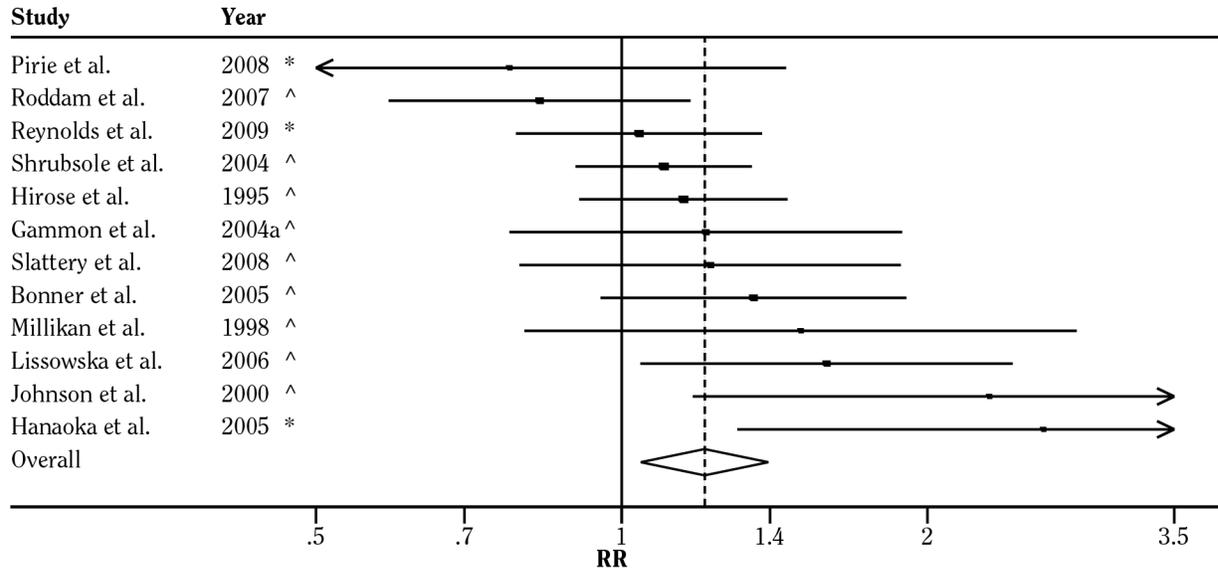
In Utero Exposure to Secondhand Smoke

Several studies have examined the possible association of in utero exposure to passive smoking with breast cancer in adulthood. Park and colleagues (2008) published a meta-analysis of seven case-control (Sandler et al. 1985b; Sanderson et al. 1996, 1998; Weiss et al. 1997; Innes and Byers 2001; Titus-Ernstoff et al. 2002; Park et al. 2006) and two cohort (Strohsnitter et al. 2005; Sanderson et al. 2006) studies of possible associations between passive exposure to maternal or paternal smoking in utero and subsequent risk of breast cancer. The summary estimate (RR) from Park and colleagues' (2008) meta-analysis was 1.03 (95% CI, 0.93–1.15) for the case-control studies and 0.59 (0.41–0.85) for the cohort studies. However, these results are difficult to interpret because the meta-analysis included a case-control study of active smoking by the participant during pregnancy and her subsequent risk of breast cancer (Innes and Byers 2001), two of the case-control studies appear to have had overlap for the diagnosis time period and geographic location (Sanderson et al. 1996, 1998), and one of the cohort studies had breast cancer mortality as an outcome (Sanderson et al. 2006). Additionally, most studies did not adequately control for potential confounders.

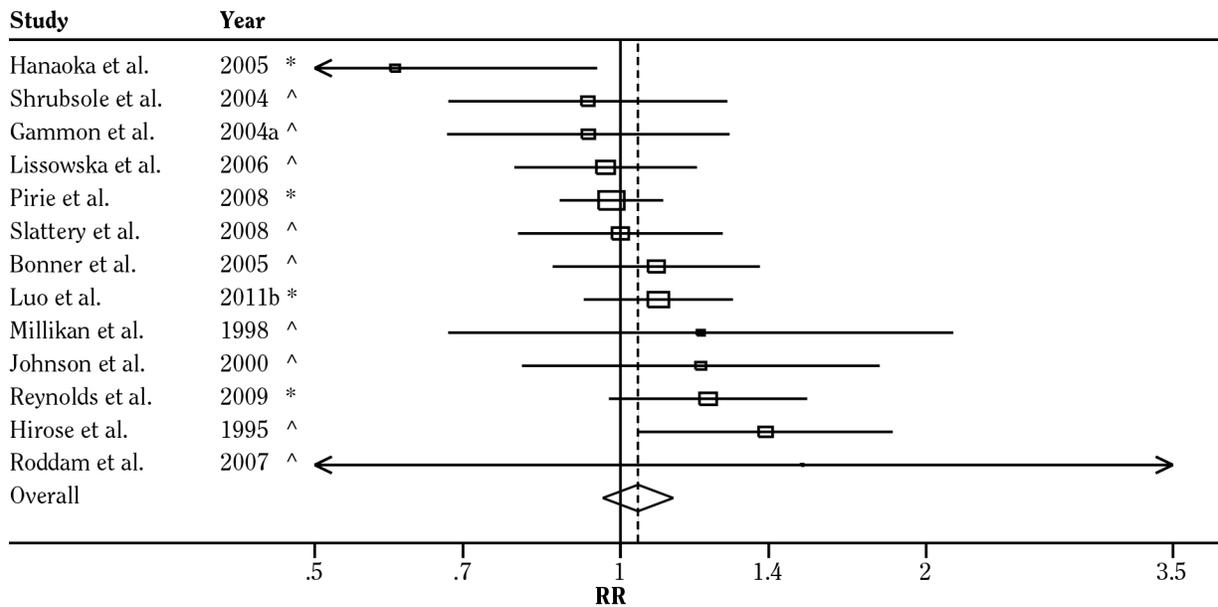
Estimates from three studies that examined in utero exposure to maternal smoking and adjusted for potential confounders in addition to age were 1.3 (95% CI, 0.9–2.1) for women, 50–64 years of age, in western Wash-

Figure 6.46 Forest plots showing the association between premenopausal (n = 12) and postmenopausal (n = 13) status for the *Most comprehensive* measure of exposure to secondhand smoke with risk for breast cancer, based on the subset of cohort and case-control studies published before 2012, excluding studies with design or analysis issues

A. Premenopausal



B. Postmenopausal



Note: * = cohort study; ^ = case-control study. See Table 6.24S, *Premenopausal*, *Postmenopausal*, for studies included in each figure and Table 6.25S (*notes e and f*) for studies excluded. Five studies were excluded from the premenopausal meta-analysis (Sandler et al. 1985a; Smith et al. 1994; Morabia et al. 1996; Delfino et al. 2000; Kruk 2007) and four from the postmenopausal meta-analysis (Sandler et al. 1985a; Lash and Aschengrau 1999; Delfino et al. 2000; Kruk 2007) because of design or analysis issues. There was one study with an estimate for only postmenopausal women (Luo et al. 2011b). Size of square is proportional to the weights used in the meta-analysis; error bars show the associated 95% CI. Solid vertical line represents the null value. Diamond represents the summary estimate and associated 95% CI. **CI** = confidence interval; **RR** = relative risk.

ington state (Sanderson et al. 1996), 1.1 (95% CI, 0.8–1.4) for women younger than 55 years of age in three areas of the United States (Weiss et al. 1997), and 1.21 (95% CI, 0.99–1.47) for women in Warsaw and Lodz, Poland, who were in most instances postmenopausal (Park et al. 2006). In the case-control study by Park et al. (2006), the risk estimate was essentially the same in participants whose mothers had smoked only at times other than during pregnancy (OR = 1.22; 95% CI, 0.81–1.84). Taken together, these studies do not provide consistent evidence that in utero exposure to secondhand smoke is associated with breast cancer.

Secondhand Smoke Exposure and Genotype Interaction

Eight case-control studies have examined potential modification of the effect of exposure to passive smoking by the NAT2 phenotype (Millikan et al. 1998; Delfino et al. 2000; Morabia et al. 2000; Chang-Claude et al. 2002; Alberg et al. 2004; Kocabas et al. 2004; Sillanpaa et al. 2005a; Conlon et al. 2010). None found statistically significant modification of effect, and results were inconsistent across studies for the direction of effect modification. Four studies suggested that risk may be increased in women with the rapid NAT2 phenotype (Millikan et al. 1998; Morabia et al. 2000; Chang-Claude et al. 2002; Kocabas et al. 2004), and three studies suggested that risk is increased with the slow phenotype (Alberg et al. 2004; Sillanpaa et al. 2005a; Conlon et al. 2010). One study (Delfino et al. 2000) reported nonsignificant findings, but numerical results were not provided. A case-only study by Lash and colleagues (2005) also reported a nonsignificant interaction that suggested increased risk in women with the slow NAT2 phenotype. Two studies (Millikan et al. 1998; Morabia et al. 2000) reported that menopausal status further modified the interaction, but they disagreed substantially in their findings. Millikan and colleagues (1998) reported an OR of 2.3 (95% CI, 0.9–6.2) in premenopausal women exposed to passive smoke who had the NAT2 rapid phenotype, as opposed to an OR of 1.2 (95% CI, 0.5–2.8) for women who had the slow phenotype. In contrast, for premenopausal women, Morabia and colleagues (2000) found that risk was not modified by phenotype; RRs were approximately 3.0 for both rapid and slow phenotypes. For postmenopausal women, Millikan and colleagues (1998) found that risk was lower in those with the rapid phenotype (OR = 0.8; 95% CI, 0.4–1.8) than in those with the slow phenotype (OR = 1.9; 95% CI, 0.7–5.2), while Morabia and colleagues (2000) reported that risk was higher in postmenopausal women with the rapid phenotype (OR = 11.6; 95% CI, 2.2–62.2) than in those with the slow phenotype (OR = 1.1; 95% CI, 0.3–4.3). Ambrosone and

colleagues (2008) performed a meta-analysis of several of these studies of exposure to passive smoking and derived a summary estimate (RR) of 1.13 (95% CI, 0.81–1.56) for slow acetylators and 1.19 (95% CI, 0.84–1.68) for rapid acetylators. Significant heterogeneity was present among the estimates, particularly for the rapid phenotype, and thus the authors did not calculate summary estimates by menopausal status.

Only a few studies have examined interactions between exposure to passive smoke and genotypes other than NAT1/2. Mordukhovich and colleagues (2010) reported that women with exposure to passive smoking were more likely to have p53-negative tumors, and Lilla and colleagues (2005) examined effect modifications by the *SULT1A1* gene using data from the same German case-control study as Chang-Claude and colleagues (2002). No statistically significant interaction was found. The study suggested a possible three-way interaction between exposure to passive smoke, *SULT1A1*, and *NAT2*, but this was not statistically significant. Millikan and colleagues (2004) found no evidence of an interaction between exposure to passive smoke and *MnSOD* on risk for breast cancer, and Gaudet and colleagues (2005) reported that risk for breast cancer increased with exposure to passive smoke regardless of the *MnSOD* genotype. In a case-only analysis, Bradbury and colleagues (2006) reported departures from multiplicative interaction for the *COM-THL* genotype and history of ever being exposed to passive smoking (OR = 2.0; 95% CI, 0.8–5.2) or of having lived with a smoker after 20 years of age (OR = 2.8; 95% CI, 0.8–10). Evaluating this result requires assumptions that the interaction is multiplicative rather than additive and that genotype and exposure are independent.

Summary and Review of Exposure to Secondhand Smoke

The 2006 Surgeon General's report on secondhand cigarette smoke concluded that there was suggestive but not sufficient evidence to conclude there was a causal association between exposure to secondhand smoke and breast cancer. It also noted that the evidence was mixed and that the positive association was observed primarily among premenopausal women in case-control studies. Since the 2006 report, 5 new cohort and 10 case-control studies have been reported for the association of passive smoking with breast cancer. Additionally, updates have been reported for 2 cohort studies and 1 case-control study.

In general, the new RRs are lower than those previ-

ously reported. For the most part, it continues to be true that case-control studies find statistically significantly increased risk of breast cancer from all or most measures of exposure, while cohort studies do not. However, the case-control studies are more heterogeneous than the cohort studies across all exposure measures. The sensitivity analyses in the present report indicate that the summary estimates are substantially reduced when case-control studies with design and analysis issues or extreme estimates are excluded. The three broadest categories of secondhand smoke exposure, *Adult—any source*, *Ever in lifetime*, and *Most comprehensive*, are associated with significant increased risks ranging from 1–15% (Table 6.25S). However, the corresponding estimates for the most restricted sensitivity analyses are not statistically significant, with risks ranging from 3–4% (Table 6.25S). Heterogeneity and publication bias also were reduced. The estimates reported for the most conservative sensitivity analyses provide an estimate that might better approximate the result if there were no publication bias and greater consistency among studies. The sensitivity analyses also reveal how certain studies leverage results. These studies are primarily smaller case-control studies, and it is not obvious that they have better quality exposure assessments. Compared with the results for active smoking, the sensitivity analyses indicate that the positive association of passive smoking with breast cancer is not statistically robust.

The meta-analyses continue to suggest that risk is mainly increased in premenopausal but not in postmenopausal women across all measures, with the exception of childhood exposure. Overall, the RRs for the most conservative summary estimates for premenopausal women are 12–26% higher than for postmenopausal women for the three broadest categories of exposure (*Adult—any source*, *Ever in lifetime*, *Most comprehensive*). However, many studies did not provide results stratified on menopausal status, and the CIs for the summary estimates were wide and overlapping (based on Tables 6.25S and 6.26S). This difference appears to be magnified by case-control studies with design or analysis issues. Thus, despite the publication of more studies, the results are inconsistent and the evidence for an association of passive smoking with breast cancer remains suggestive only in premenopausal women. To date, there are not enough published studies to evaluate associations with tumor phenotype or effect modification by susceptibility genes.

Major Summary Points on Passive Smoking

1. Based on 34 study reports published before 2012, evidence suggests that exposure to passive smoking—defined most comprehensively to include either *Ever in lifetime* or *Adult—any source* exposure—increases the RR for breast cancer by an average of 11–15%. However, sensitivity analyses suggest that this estimate should be lower because of the strong influence of 11 case-control studies with design or analysis issues. When these studies are excluded, the average increase in risk is substantially reduced to 3–4%.
2. There is emerging evidence to suggest that the risk of breast cancer from passive smoke exposure may be greater in premenopausal than postmenopausal women; 21% versus 4% for the *Most comprehensive* measure, or a relative difference of 16%.
3. There is insufficient evidence to conclude that the risk for breast cancer from exposure to passive smoking is modified by timing, source, location of exposure, estrogen receptor status, or genetic susceptibility.

Exposure to Tobacco Smoke and Breast Cancer Mortality

Smoking could influence breast cancer mortality through effects on incidence, survival, or both. In general, cancer survivors represent a high-risk population that is susceptible to multiple exposures and associated smoking-related noncancer comorbidities, such as heart disease, diabetes, obesity, sarcopenia, osteopenia, and osteoporosis (Fine et al. 1999; Twiss et al. 2001; Demark-Wahnefried et al. 2002; Rao and Demark-Wahnefried 2006; Li 2010). Some of these adverse outcomes are important contributors to mortality in women who are diagnosed with breast cancer and some are associated with cancer treatment (radiation, chemotherapy) (Rao and Demark-Wahnefried 2006; Harris 2008). Thus, a causal association between smoking and breast cancer mortality is difficult to infer because of confounders that are entangled with treatment and other noncancer, smoking-related morbidity that can contribute to mortality.

Active Smoking

In the 2004 Surgeon General's report, only one study was evaluated for the association between active smoking and breast cancer mortality (Calle et al. 1994): the CPS-II reported an increased risk for breast cancer mortality (RR = 1.26; 95% CI, 1.05–1.50) among current smokers compared with lifetime nonsmokers. The increased risk was linked to the number of cigarettes smoked per day and the number of years of smoking. The study did not find an increased risk of mortality among former smokers (RR = 0.85; 95% CI, 0.70–1.03). The 2004 Surgeon General's report suggested that this last finding dampened the other evidence because former smokers may be more likely to be screened and receive earlier diagnoses than current smokers (USDHHS 2004); consequently, these results for current and former smokers may reflect screening behavior rather than a true association (Hirayama 1984; Calle et al. 1994; Wartenberg et al. 2000).

The 2004 Surgeon General's report did not include an early report by Tverdal and colleagues (1993) on a cohort of 24,535 Norwegian women in which an RR of 0.90 (95% CI, 0.4–1.9) was estimated for breast cancer mortality from smoking more than 10 cigarettes per day. Later, the Collaborative Group Report, presenting an analysis of data from 53 studies, included an estimate for risk of breast cancer of 1.03 (SE = 0.02) in smokers who did not report alcohol consumption (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002). In New York City, Yu and colleagues (1997) conducted a study of the effect of smoking on the survival of 12,989 women diagnosed with incident breast cancer between 1990–1995, using archived data from the Memorial Sloan-Kettering Cancer Center. Among 4,580 cases, 39.4% reported ever smoking. Analyses were mutually adjusted for age, race, and histologic grade. Mortality from breast cancer was significantly increased among ever smokers (RR = 1.32; 95% CI, 1.10–1.70). Risk for mortality from breast cancer was higher among African American women (RR = 1.73; 95% CI, 1.00–2.90) than White women (RR = 1.21; 95% CI, 0.9–1.6). Follow-up was for only 5 years and no differentiation could be made between former and current smokers. In an ancillary analysis of data from the NHS-I, Egan and colleagues (2002) evaluated the association between breast cancer mortality and current and former smoking. The RR for breast cancer death was 1.19 (95% CI, 0.94–1.50) for current smokers and 1.11 (95% CI, 0.89–1.04) for former smokers. In Sweden, Manjer and colleagues (2000a) reported results for the association of smoking with breast cancer mortality in a small cohort study. A total of 792 women diagnosed with breast cancer between 1977–1986 were followed for an average of 12.1

years. The RR of breast cancer mortality in current smokers was 2.14 (95% CI, 1.47–3.10) in a comparison with nonsmokers that adjusted for age, stage at diagnosis, and other confounders.

Since the 2004 Surgeon General's report and through 2011, eight published studies have evaluated the association between smoking and breast cancer mortality (Fentiman et al. 2005; Holmes et al. 2007; Ozasa 2007; Sagiv et al. 2007; Barnett et al. 2008; Dal Maso et al. 2008; Rezaianzadeh et al. 2009; Hellman et al. 2010). Barnett and colleagues (2008) examined incident and prevalent cases; the seven other studies examined only incident cases. Each study used never smokers as the reference group and reported risk estimates for active smoking status. Two of the eight studies reported a significantly increased risk of mortality among ever smokers (Dal Maso et al. 2008; Rezaianzadeh et al. 2009). Elsewhere, Rezaianzadeh and colleagues (2009) observed that among 1,148 women who lived in Southern Iran and were followed for a median of 2.6 years, ever smokers had a 40% increased risk for mortality (95% CI, 1.07–1.86) after adjusting for family income and pathology markers, such as tumor size and grade, lymph node involvement, and metastasis. Data were collected from a hospital-based cancer registry. Detailed information about smoking status was not reported. Only 58% of the women in this group were expected to survive for 5 years, perhaps because of cultural barriers and late access to treatment (Rezaianzadeh et al. 2009). Dal Maso and colleagues (2008) observed similar results in an Italian cohort of 1,453 incident cases followed for 12.6 years: ever smokers had a 30% increased risk for mortality (RR = 1.30; 95% CI, 1.05–1.61) after adjusting for age, residential location, and year of diagnosis. Breast cancer mortality did not appear to differ between former and current smokers. Risk for smoking was somewhat higher in older women (≥ 55 years of age).

Results from the other six studies were null or inconsistent. Using a small cohort of 166 patients followed for 11 years in the United Kingdom, Fentiman and colleagues (2005) reported nonsignificant protective associations in former smokers, but increased risks in current smokers, for breast cancer-specific and disease-free survival. In contrast, Barnett and colleagues (2008), who studied a much larger cohort of 4,560 incident and prevalent cases followed for a median of 6.8 years in England, found no increased risk of mortality for former or current smokers. This study, however, did not adjust for any covariates. Holmes and colleagues (2007) examined 5,056 incident cases followed for more than 8 years in the NHS-I. After adjusting for age, use of alcohol, diet, and prognostic tumor characteristics, the study did not report

any significant associations for former or current smokers. Similarly, among 1,273 women in the Long Island Breast Cancer Study Project, Sagiv and colleagues (2007) found no significant associations between former or current smoking and breast cancer-specific mortality. In a cohort of Japanese women, Ozasa (2007) reported nearly a fivefold, statistically significant increased risk among former smokers (RR = 4.79; 95% CI, 2.18–10.5), but risk was not significantly increased in current smokers (RR = 1.43; 95% CI, 0.65–3.11). However, the study is difficult to interpret because the number of deaths was small ($n = 93$) and the CIs varied widely. Most recently, Hellman and colleagues (2010) reported results for smoking and breast cancer mortality from the Copenhagen City Heart Study, which included 528 women with a primary diagnosis of breast cancer. There was no association between breast cancer mortality and former (RR = 0.98; 95% CI, 0.77–1.24) or current smoking (RR = 1.07; 95% CI, 0.94–1.23).

Duration and Intensity of Smoking

Four studies evaluated the association between smoking duration or intensity (pack-years of smoking or cigarettes smoked per day) and breast cancer mortality. In the NHS-I, Holmes and colleagues (2007) did not find an association between an increasing number of cigarettes smoked per day (p trend = 0.77) and breast cancer mortality. Elsewhere, Dal Maso and colleagues (2008) reported a significantly increased risk in breast cancer mortality for smoking more than 25 years (RR = 1.46; 95% CI, 1.12–1.90). However, in this study, risk also increased for smokers who smoked fewer than 15 cigarettes per day (RR = 1.39; 95% CI, 1.02–1.90) but not for those smoking 15 or more cigarettes per day (RR = 1.23; 95% CI, 0.82–1.83). A similar paradoxical finding was reported by Ozasa (2007), who found a significantly increased risk in breast cancer mortality for smoking for 40 or more years (RR = 4.28; 95% CI, 1.01–18.0) but also for women who smoked fewer than 15 cigarettes per day (RR = 2.39; 95% CI, 1.04–5.51). In contrast, Sagiv and colleagues (2007) did not find an elevated risk for smoking 20 or more years (RR = 0.92; 95% CI, 0.57–1.49).

Hormone Receptor Status

Three studies analyzed the association between ER and PR status and breast cancer mortality. ER/PR status is an important predictor of breast cancer survival (Holmes et al. 2007; Sagiv et al. 2007; Dal Maso et al. 2008). In studies by Holmes and colleagues (2007) and Sagiv and colleagues (2007) and compared with ER– tumor status,

ER+ status exhibited nonsignificant protective effects on breast cancer mortality in current and former smokers. In contrast, Dal Maso and colleagues (2008) reported that ever smokers with ER+/PR+ tumor status did not have a significantly increased risk (HR = 1.11; 95% CI, 0.80–1.55) for breast cancer mortality, but the risk was increased significantly (HR = 1.90; 95% CI, 1.28–2.83) in those with other tumor phenotypes when considered as a group. It is reasonable to assume that this “other” category consisted predominantly of ER–/PR– tumors. The results for analyses stratified by menopausal status were null or inconsistent (Holmes et al. 2007; Sagiv et al. 2007).

Exposure to Secondhand Smoke

Only three studies have evaluated the association between breast cancer mortality and exposure to secondhand smoke (Hirayama 1984; Wartenberg et al. 2000; Sagiv et al. 2007). In a Japanese cohort of single-marriage, lifelong never smokers, Hirayama (1984) reported no significant associations between breast cancer mortality and the husband’s smoking status. Analyses were stratified for husband’s current versus former smoking status, duration and intensity of smoking, and age of the women at baseline and marriage. Later, Wells (1991) reanalyzed these data and reported a nonsignificant increased risk in breast cancer mortality if the husband was an ever smoker (RR = 1.26; 95% CI, 0.8–2.0). Wartenberg and colleagues (2000) analyzed data from the CPS-II cohort and reported no association of breast cancer mortality with exposure (RR = 1.0; 95% CI, 0.8–1.2) while detecting a nonsignificant increased risk among women who were married before 20 years of age to a smoker (RR = 1.2; 95% CI, 0.8–1.8). Johnson (2001) speculated that the study by Wartenberg and colleagues (2000) may have underestimated risk because it did not consider nonspousal sources and long duration of exposure. However, Wartenberg and colleagues (2001) responded that they found no increased risk among women who reported exposure at the workplace (RR = 0.8; 95% CI, 0.6–1.0) or other places (RR = 0.9; 95% CI, 0.7–1.2), and they pointed out that stratification on duration in some other studies resulted in unstable estimates because of small samples. Sagiv and colleagues (2007) examined the association between association and breast cancer using data for 1,273 cases followed for approximately 7 years in the Long Island Breast Cancer Study Project. The study found a small but nonsignificant increased risk (RR = 1.16; 95% CI, 0.63–2.15) among never-smoking women who reported ever living with a smoker.

Summary of Exposure to Tobacco Smoke and Breast Cancer Mortality

To date, the evidence is insufficient to conclude that either active or passive smoking influences breast cancer mortality. Studies have been complicated by problems with misclassifying exposure and a lack of specificity because smoking increases risk for several noncancer, comorbid conditions that contribute to mortality in survivors of breast cancer.

Evidence Synthesis

This section reviews the topic of smoking and risk for breast cancer separately for active and passive smoking, as was done in the 2004 and 2006 Surgeon General's reports. Various panels and committees have taken the same approach, providing separate reviews and conclusions about breast cancer in active and passive smokers. However, the more general question is whether exposure to tobacco smoke causes breast cancer. The review of evidence on mechanisms of breast carcinogenesis included in this chapter does not provide a basis for separating active and passive exposure. Additionally, the mechanisms that may be most prominently involved in the causation of cancer in breast tissue—that is, adduct formation and unrepaired DNA mutations—are equally applicable to active and passive smoking. In the context of the mechanism of carcinogenesis, active and passive smoking would correspond to high-dose and low-dose exposures, respectively. Consequently, this section provides a unified appraisal of the evidence on smoking, whether active or passive, and risk for breast cancer.

Methodologic Issues

The following sections summarize the methodologic issues identified in this review of published studies on the association between risk for breast cancer and either active smoking or exposure to smoking by others (passive exposure). Some of these issues are common to observational studies, but others are more specific to assessing the relationships between exposures to tobacco smoke and disease outcomes. The discussion of analytic limitations addresses the application of meta-analysis to pool and summarize data from studies with disparate designs and methods.

Information and Selection Bias

Most studies conducted to date have relied on self-reported exposure and thus information bias is a concern.

Case-control studies based on self-reported exposure are more susceptible to systematic and random error, referred to as information bias, than are cohort studies in which outcomes occur after exposure is assessed. Random misclassification of exposure attenuates risk estimates toward the null value of 1.0, thus limiting sensitivity for detecting weak but potentially causal associations. Differential misclassification between cases and controls biases risk estimates away from 1.0 in either a positive or negative direction. Some methodologic studies, however, suggest that simple measures of current smoking status are generally reported accurately. West and colleagues (2007) compared smoking misclassification rates across large, population-based surveys in England, Poland, and the United States, finding that the self-reported prevalence of current smoking was underestimated relative to the gold standard of serum cotinine level by 2.8% in England, 4.4% in Poland, and 0.6% in the United States, indicating that the extent of misclassification may vary across populations.

Misclassification of exposure to secondhand smoke may be considerably greater. Using data from Phase I (1988–1991) of the Third National Health and Nutrition Examination Survey (NHANES III), Pirkle and colleagues (1996) found significantly increased serum cotinine levels in many nonsmokers who reported no exposure to secondhand smoke at home or the workplace. Arheart and colleagues (2008) compared self-reports of tobacco use and exposures to secondhand smoke with cotinine levels using combined data from NHANES (1988–1991, 1991–1994, 1999–2000, 2001–2002, 2003–2004). Although the percentage agreement between self-reports and the cotinine data was high (87–92%) for both active smoking and passive exposure, 28% of nonsmokers who reported no exposure to passive smoke had increased levels of serum cotinine.

At present, methods are lacking for measuring long-term, cumulative exposure on either a quantitative or semiquantitative basis with high accuracy. Such measures as duration and pack-years of smoking may be subject to substantial information bias because many smokers cease and then resume smoking repeatedly over time, and their memory of the frequency and length of such episodes may not be clear. Similarly, historic childhood, long-term, and lifetime exposure to passive smoke is subject to greater information bias than are more recent adult exposures. Assessing passive exposure to smoking is further complicated by the need to account for multiple sources and locations of exposure. In addition, such passive exposure has changed at highly variable rates across regions of the United States and across other countries, further complicating assessments of long-term exposure. Compared with

cohort studies, case-control studies of passive exposure to smoking have generally included more comprehensive assessments of the timing, duration, sources, locations, and intensities of exposure. However, the results of case-control studies often display significant heterogeneity, probably reflecting varying information biases in measuring passive exposure to smoking.

Differential information bias between cases and controls can occur when disease status influences the validity of self-reported exposure, particularly if women with breast cancer are aware of the possible association of smoking with risk for breast cancer. Compared with newer studies, older studies may be less subject to differential misclassification bias because participants in those studies could have had less knowledge about the potential link between smoking and the risk for breast cancer. This may not be true for newer studies. As noted previously, some surveys have found that many women now believe that smoking is causally linked to breast cancer (Wold et al. 2005; Wang et al. 2010a).

Selection bias can create either false-positive or false-negative effects in epidemiologic studies. Consequently, studies that produce more extreme estimates should be scrutinized carefully for design issues that could produce selection bias as well as differential information bias. Several such studies were identified in this review for active smoking (Lash and Aschengrau 1999, 2002; Del-fino et al. 2000; Kruk 2007) and for passive exposure to smoking (Sandler et al. 1985a; Smith et al. 1994; Jee et al. 1999; Lash and Aschengrau 1999, 2002; Zhao et al. 1999; Morabia et al. 2000; Kruk 2007). Sensitivity analyses indicated that the results for active smoking are relatively robust, with little change in the summary estimates when these studies were excluded. This pattern did not prevail, however, for studies of passive exposure to smoking, where estimates were sharply attenuated when sensitivity analyses were conducted. Therefore, results for passive exposure to smoking may be more subject to positive bias. Finally, the funnel plots for passive smoking provide evidence of publication bias from small positive studies; small studies are statistically more likely to produce extreme estimates, and positive results are more likely to be published.

Confounding and Effect Modification

The association between smoking and breast cancer may be confounded by several established risk factors. Use of alcohol is widely regarded as one of the most important potential confounders because it is a risk factor for breast cancer (Singletary and Gapstur 2001; Boyle and Boffetta 2009) and is positively correlated with smoking (Shiffman and Balabanis 1995). However, assessments of the use of alcohol are subject to similar information biases as those

for smoking, and the strength of the correlation between smoking and alcohol use may vary with age and across populations or subgroups within a population (Caetano et al. 1998; Anthony and Echeagaray-Wagner 2000). Still, the association between use of alcohol and breast cancer is modest (RRs: 1.20–1.40), and the relationship is primarily at high levels of intake (e.g., >2 drinks/day) (Longnecker 1994; Singletary and Gapstur 2001; Boyle and Boffetta 2009), although recent reports from the Million Women Study (Allen et al. 2009) and the NHS-I (Chen et al. 2011c) suggest that risk may also be increased at lower levels of consumption. Nonetheless, the magnitude of any confounding may be trivial in populations of women with a low prevalence and level of alcohol use and/or smoking.

The Collaborative Group on Hormonal Factors in Breast Cancer and colleagues (2002) reported summary estimates of 1.09 for ever smokers, regardless of alcohol use, 1.05 when averaged across strata of alcohol use, and 1.03 when restricted to nondrinkers. The report did not evaluate associations between risk for breast cancer and duration, dose, or timing of smoking. Other than the Collaborative Group Report, no systematic analyses have compared statistical adjustment for alcohol use with restriction to nondrinkers. Most studies reviewed in this report statistically adjusted for the use of alcohol. Although residual confounding may remain after statistical adjustment, restricting analyses to nondrinkers could create selection bias if this subgroup differs systematically from drinkers in terms of smoking duration, dose, or timing. The report from the Million Women Study (Allen et al. 2009) indicates that nondrinkers were, on average, older, heavier, less affluent, less likely to exercise, and less likely to use oral contraceptives or HRT than were drinkers. While alcohol consumption was positively associated in that study with smoking overall, women who drank wine were reported to be less likely to smoke. This suggests that women who drink differ from those who do not on a variety of risk factors, including smoking.

These findings suggest that confounding between alcohol use and smoking is complex, and that restriction of the reference group to nondrinkers or that statistical adjustment for alcohol use will not necessarily result in lower risk estimates for the association between smoking and breast cancer. As noted previously, confounding can obscure associations and create either false-positive or false-negative findings. In the California Teachers Study cohort, Reynolds and colleagues (2004b) reported that the risk of breast cancer for the subgroup of current smokers who were nondrinkers was higher (RR = 1.66; 95% CI, 1.15–2.40) than the estimate for all participants after adjusting for alcohol intake (RR = 1.32; 95% CI, 1.10–1.57). In a case-control study, Li and colleagues (2005) reported

that the risk of breast cancer among current smokers who were never users of alcohol was identical to that of current smokers who consumed at least 8.2 grams of alcohol per day (OR = 1.5; 95% CI, 0.9–2.5) and was higher than that of current smokers who consumed less than 8.2 grams of alcohol per day (OR = 1.3; 95% CI, 0.7–2.3). These observations conflict with the assumption that restriction to nondrinkers or statistical adjustment for alcohol intake will result in a lower estimate of RR for smoking. Thus, the nature and extent of confounding between alcohol use and smoking for risk of breast cancer remains unresolved.

Alcohol is known to enhance the toxic effects of environmental carcinogens on some tissues, and synergy between alcohol and smoking risks has been reported for several health outcomes (IARC 2004; Lowenfels and Maisonneuve 2004). Interaction between smoking and alcohol is known to occur for some cancers, but this has not been examined with respect to breast cancer. The strongest evidence of an interaction is for tissues with direct exposure to both alcohol and tobacco smoke, such as pharyngeal and laryngeal cancers that occur in the upper respiratory tract, and esophageal cancers (Rothman and Keller 1972; Flanders and Rothman 1982; IARC 2004). However, interactions have been reported for tissues without direct exposure, such as the heart and pancreas (Lowenfels and Maisonneuve 2004). Few, if any, studies have tested for interaction between smoking and alcohol use relative to risk of breast cancer.

The use of screening mammography increased rapidly between 1987–2000, then declined or was relatively stable between 2000–2008 (Breen et al. 2011). There is evidence that health behaviors, including smoking and alcohol consumption, influence use of screening. Some studies have reported different rates of screening for smokers than for nonsmokers (Fredman et al. 1999). Trentham-Dietz and colleagues (2007b) reported that among women who reported having annual mammograms, there was an inverse association between smoking and risk for in situ breast cancer (RR = 0.82; 95% CI, 0.70–0.95), but there was no association for women who reported fewer than annual mammograms (RR = 1.04; 95% CI, 0.85–1.28), and a significant positive association for women who reported never having had a mammogram (RR = 1.48; 95% CI, 1.05–2.10). This pattern was consistent across other measures of smoking exposure, including current smoking, duration, cigarettes smoked per day, and pack-years of smoking. This provides evidence that screening behavior may modify the direction of the association of smoking with in situ breast cancer. In addition, it suggests that the association of smoking may be different for in situ than for invasive breast cancer. Of the 67 reports considered for inclusion in the meta-analyses of active smoking in

the present report, 31 (46%) specified that analyses were restricted to invasive cases only, 15 (22%) indicated that they included in situ cases, and 21 (32%) did not specify any stage-specific inclusion criteria. Estimates from studies that include in situ cases, such as those in the report by Trentham-Dietz and colleagues (2007b), may be biased toward the null or even indicate an inverse association with smoking, depending on the number of in situ cases included, due to the negative association between smoking and mammography screening. Taken together, these findings suggest that screening behavior may influence the association between smoking and risk of breast cancer. Studies conducted during the period in which there was a rapid increase in screening may be more susceptible to this influence. In addition, the association between smoking and in situ breast cancer differs from that of invasive breast cancer. Thus, analyses of the association between smoking and risk for breast cancer should account for mammography screening.

Wells (1991) and others (Morabia et al. 1996) proposed that the association between smoking and breast cancer is attenuated when passively exposed women are included in the reference group. As a result, several studies have used never smokers who reported no passive exposure as the reference group (no active/no passive). Results from these studies, however, are inconsistent and the meta-analyses suggest only a small difference between summary estimates based on *no active* exposure groups and those where the reference groups were no active/no passive exposure. Two issues should be considered: (1) the no active/no passive exposure reference group is typically very small and highly selected, which may affect estimates of precision and bias; and (2) passive exposure is difficult to define clearly, especially over time, resulting in misclassification bias. These issues would be more significant if women systematically overreport passive exposure and underreport active smoking, as postulated by Trichopoulos and Lagiou (2004).

The association between risk for breast cancer and smoking could be most apparent among women who initiated smoking before their first pregnancy because of the increased susceptibility of breast tissues to carcinogens before terminal differentiation. However, timing in relation to first pregnancy may be confounded with age at first pregnancy, because older age at first pregnancy is an independent risk factor for breast cancer. Only one-half of the studies that estimated risk for smoking before first pregnancy adjusted for age at first pregnancy (Innes and Byers 2001; Egan et al. 2002; Al-Delaimy et al. 2004; Gram et al. 2005; Lissowska et al. 2006; Ha et al. 2007; Magnusson et al. 2007; Prescott et al. 2007; Young et al. 2009; Luo et al. 2011b; Xue et al. 2011). It is also unclear whether

smoking during pregnancy has a different association with risk for breast cancer than smoking before first full-term pregnancy.

Many studies have examined modification effects of smoking by genes that influence susceptibility to smoking-related carcinogens. Specific groups of candidate genes have been studied that influence carcinogen metabolism, oxidative stress, and DNA repair. Some studies have been more concerned with establishing main effects of genetic variants than with the modification effects of smoking (e.g., Metsola et al. 2005), and few studies have had adequate statistical power to detect interactions. Some studies and meta-analyses provide support for *NAT2* as a genetic variant that modifies smoking risk, but there is little consistent evidence for other genetic variants. Associations between risk for breast cancer and active smoking and passive exposure to smoking could differ according to breast cancer phenotype. Mixing different breast cancer phenotypes may attenuate or distort risk estimates for smoke exposure, especially if underlying mechanisms differ and these phenotypes have different sets of potential confounders. Results stratified by ER status have been inconsistent for active smoking, and only a few studies have evaluated passive exposure to smoking. Sample sizes and statistical power are a problem for these studies because of the relative rarity of the ER-phenotype.

Limitations of Meta-Analysis

For the meta-analyses in this report, estimates from some studies had to be pooled across various strata, including exposure, age, menopausal status, and race/ethnicity; this may have obscured variation across these strata in some studies. Similarly, estimates across categories of exposure to passive smoking had to be pooled to obtain usable estimates for some studies. The net result of this pooling smoothed out variation across strata within some studies that may have been due to real differences, or it could have been likely due to chance. Consequently, the summary estimates from the meta-analyses should be regarded as conservative. Calculating estimates for subgroups in meta-analyses is difficult when studies use different classification criteria or cutoffs for stratification; this was a problem for analyses of timing and the duration of active smoking. In addition, tests for heterogeneity and bias are imprecise and potentially misleading when there are few studies in a subgroup (Sterne and Harbord 2004). Although results for the broadest exposure categories are precise, they may obscure important differences between subgroups. Conversely, effects within subgroups that contain few studies are imprecise and more susceptible to bias, which is difficult to evaluate.

Criteria for Causal Inference

In keeping with Surgeon General's reports since 1964 (USDHEW 1964), this section addresses the evidence for a causal association between tobacco smoke and risk for breast cancer according to the criteria previously used—including consistency across studies, temporal relationship of association, strength of the association, and the biologic plausibility of the association.

Consistency

The replication of associations across studies that differ with regard to study design, study population, and investigators provides evidence of consistency. When all cohort studies prior to 2012 and case-control studies published from 2000 through 2011 were considered together in a meta-analysis of active smoking, significant heterogeneity was found for the effect of ever smoking. When cohort and case-control studies were separated, this heterogeneity was confined to the case-control studies and could be attributed largely to two studies with extreme estimates. The meta-analyses examining the risk of breast cancer with former and current smoking, duration of smoking, cigarettes smoked per day, and 20 or more pack-years of smoking indicated no statistically significant heterogeneity for these variables among either cohort or case-control studies, whether considered separately or when taken together. Results for age at smoking initiation and smoking before first pregnancy were less consistent, with significant heterogeneity among case-control studies. Overall, the summary estimates for case-control and cohort studies were generally in agreement and consistent across exposure categories for active smoking.

Results from the studies of passive exposure to smoking were less consistent, with greater contrasts between cohort and case-control studies for both individual and summary estimates. Cohort studies have generally produced null findings and case-control studies have tended to produce positive results. Case-control studies exhibited significant heterogeneity and evidence for publication bias from small studies. Small studies are more likely than larger ones to produce extreme estimates due to chance. The sensitivity analyses tabulated in Tables 6.25S and 6.26S indicate that estimates for most categories of passive exposure are attenuated when small studies, those with design or analysis issues, and studies with extreme outlier estimates are all excluded.

There is persistent evidence to suggest that the associations between active smoking and passive smoke exposure and breast cancer are stronger in premenopausal than in postmenopausal women. While the magnitude of

the difference in risk between premenopausal and postmenopausal women may differ by study design, it is consistent across both case-control and cohort studies (Tables 6.18S and 6.25S). In the 2006 Surgeon General's report, the summary RR for the most comprehensive measure of smoking was 1.64 in premenopausal *versus* 1.00 in postmenopausal women (Table 6.25S). Since then, several new and larger studies of passive smoking, including cohort studies, have found substantially lower estimates for premenopausal women, compared with studies published through 2005 and reviewed in the 2006 Surgeon General's report. Nonetheless, the difference in risk between premenopausal and postmenopausal women remains. However, it is difficult to discern why the association between risk for breast cancer and passive smoke exposure should be stronger than that for active smoking in premenopausal women.

Table 6.27S summarizes results for active smoking and passive exposure to smoking by study design and exposure category. The table permits a ready comparison of estimates for *Ever smoker* and *Most comprehensive* as the broadest categories for active smoking and exposure to secondhand smoke, respectively. Table 6.27S also shows results for the most conservative sensitivity analyses for these categories and for both random and fixed-effect models. The summary estimates from cohort studies and case-control studies are markedly similar across all measures of active smoking and affected little by exclusions in sensitivity analyses. Thus, the overall evidence is relatively consistent for a weak effect of active smoking on risk for breast cancer. The evidence is less consistent for passive exposure to smoking, with marked differences between case-control and cohort studies and greater sensitivity to exclusions for design and analysis issues, sample size, and extreme estimates.

Temporality

Cohort studies are generally regarded as providing stronger evidence than case-control studies for causality because they satisfy the temporality criterion that the measurement of exposure precede the ascertainment of the outcome. Cohort studies published since 2000 generally show a small increased risk for breast cancer associated with active smoking (Manjer et al. 2000b; Egan et al. 2002; Al-Delaimy et al. 2004; Reynolds et al. 2004b; Gram et al. 2005; Olson et al. 2005; Cui et al. 2006; Ha et al. 2007; Luo et al. 2011b; Xue et al. 2011). All of these cohort studies found RRs greater than 1.0, and several reported significantly increased risk for breast cancer across multiple measures of smoking exposure.

The summary RRs from the most restricted meta-analyses of active smoking for cohort studies are 1.10 for ever smokers, 1.09 for former smokers, 1.14 for current smokers, 1.15 for smoking 20 or more years, 1.12 for 20 or more cigarettes smoked per day, and 1.15 for 20 or more pack-years of smoking (Table 6.27S). In contrast, the summary RRs for the most restricted analyses for cohort studies that included an assessment of exposure to passive smoking have generally been null, with estimates of 1.01 for *Adult—any source*, 1.02 for *Ever in lifetime*, and 1.02 for *Most comprehensive* (Table 6.27S). Taken together, the results from cohort studies support an association between risk of breast cancer and active smoking of long duration but do not provide similar evidence for an association with passive smoking.

With regard to timing, results to date do not support the hypothesis that active smoking or passive exposure to smoking have greater carcinogenic effects during periods when breast tissues are less differentiated and theoretically more susceptible. Summary risk estimates from cohort and case-control studies combined are significantly increased for early age at smoking initiation (20 years of age and younger) and smoking before/during first pregnancy (RRs = 1.11 and 1.10, respectively), but of similar magnitude to current smoking (RR = 1.12), former smoking (RR = 1.09), or ever smoking (RR = 1.09) (Table 6.17S). Results for exposure to passive smoking during childhood were generally null, regardless of study design (Table 6.26S).

Strength of Association

The results of the meta-analyses for active smoking indicate weak associations, ranging from 9% for the most restricted analysis of ever smoking to 16% for 20 or more years of smoking. The associations for various measures of passive exposure to smoking were similarly weak, 4–14% for the *Most comprehensive* measure, depending upon exclusions and sensitivity analysis. Considering these modest increases, it is not surprising that most studies, particularly in stratified analyses, have not had sufficient statistical power to detect an increased risk. Inconsistent results across studies with different designs and degrees of selection and information bias are not unusual for a risk factor with a weak effect. Given the relatively weak associations, confounding and bias are important concerns.

Mixing genetic subpopulations with different levels of susceptibility can attenuate or obscure the overall associations, but little headway has been made in identifying such subgroups, with the possible exception of *NAT2*. Larger studies are needed to clearly establish the modifi-

cation of effect by genetic susceptibility. If either active smoking or exposure to passive smoking has a causal but weak association with risk for breast cancer, then defining a dose-response gradient of effect will be difficult without more precise measurement of exposures and larger samples.

The evidence to date is not definitive for a dose-response relationship with measures of exposure for active smoking or for exposure to tobacco smoke. Findings are inconsistent with regard to trends across exposure levels (e.g., duration, cigarettes smoked per day, or pack-years of smoking), and only a few reports have formally tested the trends. The meta-analytic results provide weak evidence for a biologic gradient for active smoking in that summary estimates (Table 6.17S) are slightly higher for current smokers (RR = 1.12) than former smokers (RR = 1.09) and highest for smoking 20 or more years (RR = 1.16), 20 or more cigarettes smoked per day (RR = 1.13), and accumulating 20 or more pack-years of smoking (RR = 1.16). Quantifying the cumulative dose of secondhand smoke is complex because the assessment should consider multiple sources and locations of exposure in addition to duration. Evidence from recent cohort studies is mixed (Reynolds et al. 2009; Luo et al. 2011b; Xue et al. 2011).

Biologic Plausibility

This chapter and the 2010 Surgeon General's report have addressed tobacco smoke carcinogenesis and mechanisms by which smoking may increase breast cancer risk. Multiple lines of evidence support the biologic plausibility of a causal relationship of tobacco smoke with breast cancer.

Studies have confirmed the presence of short-term biomarkers stemming from exposure to tobacco smoke, such as cotinine, in breast tissues and fluids (Petrakis et al. 1978). Carcinogen-DNA adducts, which are widely regarded as providing one of the best biomarkers of exposure effect (Lodovici and Bigagli 2009), have also been consistently detected in breast tissues and body fluids of smokers (Perera et al. 1995).

The evidence for an anti-estrogenic effect of smoking on breast cancer is weak, leading some to question whether this is a valid explanation for a few studies that have reported inverse associations or for the attenuation of the carcinogenic effects of tobacco smoke (Palmer and Rosenberg 1993). Baron (1996) reviewed evidence for this hypothesis in relation to several hormone-related cancers but found the data for breast cancer to be inconclusive. Studies of the effects of smoking on hormone metabolism and circulating levels have been inconsistent, and mechanisms for an anti-estrogenic effect in breast cancer are

not well established (USDHHS 2004). However, a recent reanalysis of 13 prospective studies including approximately 6,000 postmenopausal women reported that both estrogen and androgen levels were increased in women who smoked 15 or more cigarettes per day (Endogenous Hormones and Breast Cancer Collaborative Group 2011).

Conclusions

1. The evidence is sufficient to identify mechanisms by which cigarette smoking may cause breast cancer.
2. The evidence is suggestive but not sufficient to infer a causal relationship between tobacco smoke and breast cancer.
3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer.
4. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer.

Implications

Sufficient quantitative evidence indicates that smoking—active smoking or passive exposure to smoking—is associated with an increased risk for breast cancer. However, the magnitude of risk is small, and neither active smoking nor passive exposure to smoking constitutes a large risk to the breast health of women. Nonetheless, reducing exposure to tobacco in women is a potential avenue for reducing the burden of breast cancer. Because breast cancer is the most frequent type of cancer in women and accounts for significant morbidity and mortality, research should continue to examine potential causes, including tobacco smoking and exposure to secondhand smoke.

Approximately 20% of women in the United States smoke, with prevalence varying by region (see Chapter 13). Prevalence also varies substantially by race/ethnicity. Over the past two decades, smoking prevalence has declined more rapidly in older age groups than in younger age groups, although the prevalence of smoking among 18- to 25-year-old women is also declining. As a result, prevalence rates do not differ much between women 45–64 years of age and those 18–44 years of age. Selfreported prevalence of exposure to secondhand smoke among

nonsmoking adults also varies widely among the states, from a low of 3.2% in Arizona to a high of 10.6% in West Virginia for exposure at home, and from a low of 6.4% in Connecticut to a high of 11.4% in North Carolina for exposure at the workplace (CDC 2009a). Internationally, the prevalence of smoking among women is not high in some countries (e.g., China, Japan, and Korea) (Table 6.13), but women's exposure to secondhand smoke is pervasive because of high rates of smoking among men (Mackay and Eriksen 2002; WHO 2002).

The extensive review in this chapter indicates that more research should be carried out on the association between tobacco smoke and risk for breast cancer, addressing several specific issues. Further research should explore the risk of exposure in genetically defined subgroups. Genomewide association studies that exam-

ine the interaction of multiple genes with smoking and biomarkers of tobacco exposure will undoubtedly be conducted in the future (Taioli 2008). Given the variety and scope of methodologic limitations identified in this review, larger cohort studies are needed that incorporate the best and most complete methods of measuring exposure, including exposure biomarkers and genetic susceptibility markers, and that oversample younger women and minorities to address the important questions of timing with respect to first pregnancy and smoking in relation to different breast cancer phenotypes. Although these additional population studies are warranted, researchers also need to gain a deeper understanding of the underlying mechanisms between exposure and disease incidence to provide a stronger framework for interpreting epidemiologic evidence.

Adverse Health Outcomes in Cancer Patients and Survivors

As survival from cancer has improved over time, the question of the potential impact of cigarette smoking on cancer patients and survivors is of increasing relevance. This topic is of growing importance, because survival following the diagnosis of many types of cancer has improved markedly during the past decades, such that the prevalence of cancer survivors in the United States is now more than 14 million and increasing (Siegel et al. 2012). This section reviews the evidence concerning cigarette smoking as a risk factor for adverse health outcomes in cancer patients during treatment and their survivorship.

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports have not specifically evaluated the evidence concerning cigarette smoking and adverse health outcomes in cancer patients. The reports have concluded that there is sufficient evidence to infer that cigarette smoking causes premature death; multiple diseases, including multiple types of malignancy and other adverse health effects; and an overall diminished health status, which predisposes cigarette smokers to diverse nonspecific consequences. These findings apply both to cancer patients (i.e., those in the course of diagnosis and treatment) and survivors (i.e., those who have completed treatment). The 2010 Surgeon General's report, *How Tobacco Smoke Causes Disease*, detailed the

many mechanisms leading to these adverse health effects (USDHHS 2010). Thus, the evidence from previous Surgeon General's reports provides a foundation for this review, which is the first in this series of reports to address the consequences of smoking for cancer patients, including the impact of smoking on cancer-specific outcomes such as recurrence, response to treatment, and toxicities from treatment.

Biologic Basis

For the purposes of this review, "adverse health outcomes" refers to a suite of unfavorable outcomes. The adverse effects of smoking on survival after a diagnosis of cancer could involve treatment-related effects on the tumor (e.g., accelerated growth, progression, metastases, and recurrence), or on the response to treatment (either tumor resistance or treatment-related toxicities). In addition, patients being treated for a cancer are likely to have a greater frequency of other diseases caused by smoking, such as coronary heart disease or chronic obstructive pulmonary disease (COPD), and hence tolerate treatment less well than nonsmokers who are generally healthier. In addition, overall survival following a diagnosis of cancer will reflect the greater risk of smokers for death from any cause (see Chapter 12, "Smoking-Attributable Morbidity, Mortality, and Economic Costs"). A description of the biologic basis of the association for each of these potential

outcomes is beyond the scope of this section. However, relevant material on mechanisms of carcinogenesis, disease pathogenesis, and nonspecific effects has received extensive coverage in earlier reports, particularly the 2010 report, and elsewhere in this report (see Chapter 10, “Other Specific Outcomes”).

With respect to all-cause mortality, the mortality burden from smoking is largely attributable to its role in causing multiple types of cancer, cardiovascular disease, and COPD. Many aspects of the pathogenesis of these diseases in smokers have been characterized, and these same mechanisms would apply to people with cancer and to cancer survivors. As detailed in the 2004 Surgeon General’s report, in addition to causing specific disease endpoints, cigarette smoking causes systemic inflammation and oxidative stress and has widespread and complex effects on immune function (USDHHS 2004). The 2004 report concluded that smoking causes overall poorer health status, leaving smokers with a diminished health status compared to nonsmokers. This diminished health status represents a nonspecific pathway by which cigarette smoking could affect cancer outcomes, such as through increased treatment-related toxicities.

There are also specific biologic lines of evidence to suggest that cigarette smoke could promote tumor development, leading to increased risk for cancer recurrence and lack of response to treatment (USDHHS 2010). The 2010 Surgeon General’s report sets out multiple mechanisms by which smoking leads to loss of control of cell replication. In mice engrafted with Lewis lung cancer cells, treatment with cigarette smoke increased tumor size and vascular development (Zhu et al. 2003). In colon cancer cells, cigarette smoke extract (CSE) increased cell proliferation and the level of activation of cyclooxygenase-2 (COX-2) (Liu et al. 2005). In this *in vitro* model, CSE also increased proliferation and expression of VEGF and MMP expression, which are associated with increased angiogenesis and tumor invasion (Ye et al. 2005b). Momi and colleagues (2013) showed that cigarette smoke increased tumor growth and metastases in pancreatic cancer cells. Inhibition of lipoxygenase or COX-2 partially prevented the increase in tumor growth associated with CSE treatment in colon cancer xenografts (Ye et al. 2005a). Signal transduction through activation of AKT has been implicated as a significant contributor to tobacco-carcinogen induced tumor formation (Memmott and Dennis 2010). Pancreatic ductal cells treated with CSE have decreased autophagy modulated through activation of AKT (Park et al. 2013). An and colleagues (2012) observed that in lung cancer or head and neck cancer cells, CSE induced activation of AKT leading to decreased response to chemotherapy and increased efflux of chemotherapy from cancer

cells. Collectively, these studies demonstrate tumor-promoting activities of cigarette smoke that could contribute to cancer recurrence and lack of response to treatment.

Not all tissues are exposed to the same mixture of tobacco smoke components. However, nicotine does reach all organs through deposition of nicotine-laden particles, absorption, and systemic circulation; consequently, there has been great interest in nicotine as a possible tumor promoter. The potential role of nicotine, and activation of the nicotinic acetylcholine receptor (nAChR), in promoting tumor growth has been extensively studied and was addressed specifically in the 2010 report and in Chapter 5, “Nicotine,” of this report. Cigarette smoke can activate systemically expressed nAChRs that are present in both normal and cancerous tissues (Dennis et al. 2005; Hukkanen et al. 2005; Singh et al. 2011; Schuller 2012). Several recent reports support the role of nicotine nitrosamines—such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol—as well as activation of nAChRs and β -adrenergic receptors in contributing to a more aggressive tumor phenotype, as defined by increased proliferation, angiogenesis, migration, invasion, and epithelial-to-mesenchymal transition (Schuller 2008, 2012; Singh et al. 2011; Warren and Singh 2013). The 2010 report (p. 10) concluded that “There is consistent evidence that smoke constituents...nicotine and methyl (4-nitrosamino)-1-(3-pyridyl)-1-butanone can activate signal transduction pathways directly through receptor-mediated events, allowing the survival of damaged epithelial cells that would normally die.” Further, nicotine and its activation of the nAChRs may decrease the effectiveness of cancer therapies both in *in vitro* models and *in vivo* (Dasgupta et al. 2006; Treviño et al. 2012; Warren et al. 2012; Banerjee et al. 2013). A specific role for nicotine as a determinant of therapeutic response in cancer patients has not yet been identified. In an *in vitro* model, removing nicotine does not appear to reduce the carcinogenic effect of cigarette smoke (Jorgensen et al. 2010); and nicotine replacement therapy has no appreciable effect on the development of cancer (Murray et al. 2009).

Epidemiologic and Clinical Evidence

Literature Search and Other Methodologic Considerations

The literature search strategy for this wide-ranging review was designed to have high sensitivity, by casting as broad a net as possible in searching the MEDLINE database and then manually identifying articles with evidence

on the association between adverse outcomes in cancer patients and smoking. For example, an initial search comprised key terms that included (“cigarette*” OR “smok*” OR “tobacco”) and (“cancer” OR “neoplasm”). Due to the limited data available prior to 1990 and the tremendous changes that have occurred in treatment of cancer patients over time, the search only yielded studies published in 1990 through October 2012. As the relevant evidence accumulated, it was found to be concentrated on the specific topics of the associations between cigarette smoking and (1) overall mortality/survival; (2) cancer-specific mortality/survival; (3) risk of second primary cancers; (4) cancer recurrence/response to treatment; and (5) toxicity associated with cancer treatment. Consequently, for this chapter, the term “adverse health outcomes” represents a suite of outcomes listed above. The evidence was reviewed for each of these topics. Due to the large total numbers of relevant studies, a restriction was made based on sample size for the articles included in the evidence tables. Thus, studies of less than 100 patients were excluded from this evidence review for all disease sites except head/neck and lung where substantially more studies have been performed; thus for head/neck and lung only studies with at least 200 patients were included. In select cases, studies with fewer patients were included if the disease site was rare (such as vulvar or anal cancer) or if a unique finding was present (such as studies evaluating smoking cessation). Only data from original research reports were included in the summary tables, whereas relevant systematic reviews and meta-analyses are discussed within the text but not included in the evidence tables.

Some methodologic issues were applicable across the range of outcomes addressed. First, all evidence was obtained prospectively, such that the measurement of cigarette smoking preceded the occurrence of the health outcomes. Smoking information was collected either via review of medical records or a systematic protocol directly from patients.

Further, the classification of smoking status varied widely across studies, from never/former/current smoking status to current/noncurrent to ever/never and many other classification schemes. In assessing the consequences of smoking, a reference group of never smokers is preferred, although this reference group was not available for all studies. If multiple comparisons were presented, the classification of never/former/current smoker was preferentially included in the summary tables.

A feature common to all of the study populations is that they were composed of cancer patients, but represented a very diverse set of clinical diseases. The observational studies are also complicated by the differing outcomes, which include cancer-free survival, mortality from cancer, and all-cause mortality, ranging from highly

specific to very general. For the purposes of this evidence review, unless it was critical to making inferences, such as for the risk of second primary cancers, the approach was to interpret the body of evidence as a whole without looking for variation in the consequences of smoking by type of malignancy, tumor site, or stage of disease.

Cigarette Smoking and All-Cause Mortality in Cancer Patients

Studies in cohorts of cancer patients that assessed the association between cigarette smoking and all-cause mortality are summarized in Table 6.28S, which includes the results from 159 different studies. These studies varied widely in design, sample size and composition, and duration of follow-up. For example, sample sizes ranged from the minimum of 64 (in an anal cancer study) to more than 20,000, follow-up periods ranged from less than 1 year to more than 10 years, and the populations studied included patients with a single type of cancer as well as cohorts comprised of patients with a diverse array of malignancies. Despite the diversity of research approaches, associations indicative of increased risk associated with smoking were observed in most studies (87% or 139/159). Further, statistically significant increased risks were observed in 62% (99/159) of the studies. There was considerable variation in the magnitude of the association between cigarette smoking and all-cause mortality, but in 83 of the studies at least a 50% increase in mortality was observed among cigarette smokers, either overall or in at least one subgroup, compared with never or nonsmokers. These associations are of similar magnitude to the association of smoking with all-cause mortality in general population cohorts (see Chapter 11, “General Morbidity and All-Cause Mortality”).

In 35 studies in which RRs were presented for current smokers and former smokers compared with never smokers, the median RRs were 1.22 for former smokers and 1.51 for current smokers. In six of the eight studies that presented the results in a way that allowed for assessment of dose-response, death rates increased with the number of cigarettes smoked (Boffetta et al. 1997; Talamini et al. 2008; Toyooka et al. 2008; Janjigian et al. 2010; Hung et al. 2012; Kawakita et al. 2012), but consistent dose-response trends were not observed in two studies (Dikshit et al. 2005b; Dal Maso et al. 2008). All eight of these studies categorized the data across three categories, and using the lowest category as the referent category (RRs = 1.0), the median RRs for the middle and high categories were 1.48 and 1.75, respectively.

The RRs for all-cause mortality in former smokers was intermediate, between that for never smokers and that for current smokers, suggesting that smoking cessation prolongs survival compared to persistent smoking.

Some studies provide evidence to directly assess whether smoking cessation reduces the mortality rate compared to persistent smoking. Chen and colleagues (2010b) observed that quitting smoking after a cancer diagnosis was associated with significantly reduced risk of death compared to persistent smoking. In a longitudinal study of 264 head and neck cancer patients, Mayne and colleagues (2009) observed that, compared to nonsmokers, the RR among those who remained persistent smokers was in the direction of increased risk (RR = 1.83; 95% CI, 0.85–3.94); whereas among those who had refrained from smoking at any time during follow-up, the RR indicated decreased risk (RR = 0.36; 95% CI, 0.10–1.31). In a meta-analysis comparing lung cancer patients who remained persistent smokers to those who stopped smoking, Parsons and colleagues (2010) observed that persistent smoking was associated with RRs of all-cause mortality in the direction of increased risk in non-small cell lung cancer patients (unadjusted: 4 studies, summary RR = 1.19; 95% CI, 0.91–1.54; adjusted: one study [Nia et al. 2005] RR = 2.94; 95% CI, 1.15–7.54) and in small cell lung cancer patients (unadjusted: two studies, summary RR = 1.18; 95% CI, 1.03–1.36; adjusted: one study [Videtic et al. 2003] RR = 1.86; 95% CI, 1.33–2.59). Not all reported associations were statistically significant, but the direction of the associations was consistent in indicating that the all-cause mortality rate in cancer patients, who were smokers at the time of diagnosis, is greater in those who remain smokers after diagnosis compared to those who quit.

Cigarette Smoking and Overall Survival in Cancer Patients

Overall mortality and overall survival are complementary in assessing the endpoint of vital status; but, because the numerical results differ, the results for overall survival are presented separately in Table 6.29S for clarity. The results of 62 studies, in cohorts of cancer patients that reported on the association between cigarette smoking and overall survival, are summarized in Table 6.29S. The results of 77% (48/62) of these studies indicated that cigarette smoking was associated with shorter survival after a diagnosis of cancer; for 42% (26/62) of the total studies, the results were statistically significant. For 6 of the studies of overall survival, the results were reported in the text as not statistically significant without providing the estimated effect, so the direction and magnitude of the associations observed in those studies cannot be determined. In the 4 studies in which the RRs were presented for current and former smokers relative to never smokers, the median survival was 19% less in former smokers and 31% less in current smokers. Ang and colleagues (2010) reported a statistically significant trend of 1% worse sur-

vival for each additional pack-year of smoking ($p = 0.002$). With respect to whether smoking cessation is associated with prolonged survival, Jerjes and colleagues (2012) followed a cohort of oropharyngeal cancer patients and found better survival at 3 and 5 years after diagnosis for those who quit smoking successfully.

Cigarette Smoking and Cancer Mortality in Cancer Patients

The studies conducted in cohorts of cancer patients that assessed cigarette smoking in relation to cancer-specific mortality or cancer-specific survival are summarized in Table 6.30S. The results are stratified according to whether the study outcome was cancer mortality or cancer survival (Table 6.30S). Of the 58 studies of cancer mortality, 79% (46/58) documented a higher mortality rate in smokers and the association with smoking was statistically significant in 59% (34/59) of the studies. In 15 studies in which the RRs were presented for current and former smokers relative to never smokers, the median RR was 1.03 for former smokers and 1.61 for current smokers. Three studies reported evidence on the presence of a dose-response relationship, with 1 study showing a monotonic gradient (Marks et al. 2009) and 2 others not showing such a gradient (Dal Maso et al. 2008; Toyooka et al. 2008). Nine of the 15 studies yielded results in the direction of poorer cancer-specific survival associated with cigarette smoking (Table 6.30S).

Cigarette Smoking and Risk of Second Primary Cancers in Cancer Patients

The studies in cohorts of cancer patients that assessed cigarette smoking in relation to risk of developing a second primary cancer are summarized in Table 6.31S. The results of these 26 studies uniformly indicated a positive association of cigarette smoking with increased risk of developing second primary cancers. Not surprisingly, the strongest associations were observed when lung cancer or another smoking-caused cancer was considered as the second primary cancer of specific interest. For example, in studies of lung cancer as a second primary cancer that had a referent category comprised of former smokers or never smokers, the RRs of developing lung cancer as a second primary were elevated from 6-fold to 24-fold (van Leeuwen et al. 1995; Obedian et al. 2000; Ford et al. 2003; Gilbert et al. 2003; Kaufman et al. 2008). Similarly, the results for other malignancies, known to be caused by cigarette smoking, were consistently in the direction of increased risk. Higher risk was observed when the smoking-caused cancers were grouped (Park et al. 2007) or specific malignancies were considered, such as head and neck cancer (Barbone et al. 1996), esophageal cancer (Rossini

et al. 2008), and bladder cancer (Boorjian et al. 2007). The strongest associations tended to be observed when the specific second primary cancer studied was known to be causally associated with active smoking, but the increased risk of any second primary cancer associated with cigarette smoking was still robust. For example, in the 5 studies not specific to smoking-caused cancers that classified smoking as never/former/current, the median RR of second primary cancers was 1.20 for former smokers and 2.20 for current smokers. Four studies assessed dose-response relationships, and all showed evidence that the risk of a second primary cancer increased as the amount of smoking increased (Hiyama et al. 1992; Barbone et al. 1996; Dikshit et al. 2005a; Leon et al. 2009).

Evidence of a synergistic interaction between smoking status and treatment with radiation therapy was observed, with smokers who were treated with radiation therapy having a greater risk of second primary cancers compared to smokers not treated with radiation therapy. In a case-control study of patients with breast cancer plus lung cancer (cases), compared to breast cancer alone (controls), compared to former smokers not exposed to radiation therapy, the RR of lung cancer in current smokers not treated with radiation therapy was 6.0 (95% CI, 3.6–10.1) and in current smokers treated with radiation therapy the RR was 9.0 (95% CI, 5.1–15.9) (Ford et al. 2003). In another case-control study of lung cancer among patients with Hodgkin's disease, risk factors were addressed in a case group (lung cancer and Hodgkin's disease) compared to a control group (Hodgkin's disease alone) (Travis et al. 2002). Risk for lung cancer was assessed for a category of "heavy smokers" (at least one pack or more per day) compared with a category that included lighter smokers and nonsmokers together. There was some indication of greater lung cancer risk associated with both chemotherapy and radiation for those in the heavy smoker category. In a study of bladder cancer following prostate cancer, current smoking was associated with the expected doubling in bladder cancer risk, but the risk was 3.6-fold among current smokers treated with radiation therapy (Boorjian et al. 2007).

Cigarette Smoking and Recurrence and Response to Treatment in Cancer Patients

Tables 6.32S and 6.33S summarize studies in cancer patients that assessed cigarette smoking and risk of recurrence (Table 6.32S) and risk for lack of treatment response (Table 6.33S). Recurrence was defined as a second cancer in the same anatomic site as the original primary cancer diagnosis. Of the 51 studies that reported on the association between cigarette smoking and the risk of

recurrence, 82% (42/51) had results showing either a statistically significant association and/or a ≥ 1.2 -fold RR estimate; 53% (27/51) showed elevated risks of recurrence in smokers that were statistically significant. In the 11 studies that classified smoking status as never/former/current, the median RR of recurrence was 1.15 for former smokers and 1.42 for current smokers. Of the three studies that reported evidence of presence of a dose-response relationship (Guo et al. 2009; Marks et al. 2009; Hung et al. 2010), in 2 of the studies there was a consistent increase in risk of recurrence with greater amount smoked (Guo et al. 2009; Hung et al. 2010). The results of the study of Fleshner and colleagues (1999), as recalculated by Aveyard and colleagues (2002), estimated that in bladder cancer patients the RR of recurrence was 0.71 (95% CI, 0.48–1.05) in those who stopped smoking compared to persistent smokers.

The specific outcomes included under response to treatment (Table 6.33S) varied and included progression-free survival, complete response, metastasis, local control, and persistent disease. Of the 16 studies addressing cigarette smoking and these outcomes, in 72% (13/18) cigarette smoking had a statistically significant association with a worse response. In 1 study, a dose-response trend was observed, indicating that smoking decreased progression-free survival in head and neck cancer patients by 1% per pack-year of smoking (95% CI, 1.00–1.01; $p = 0.002$) (Ang et al. 2010).

Cigarette Smoking and Toxicity Associated with Cancer Treatment

Studies in cohorts of cancer patients that addressed the association between smoking and cancer treatment-related toxicity are summarized in Table 6.34S. Of the 82 studies that included results for the association between cigarette smoking and treatment-related toxicities, 94% (77/82) showed a positive association between smoking and increased toxicity, with 80% (66/82) statistically significant. Of the 49 studies that used a category of current smoking, 88% (43/49) showed a statistically significant positive association between current smoking and toxicity.

Continued smoking after treatment with radiotherapy increases risk for hospitalization and toxicity compared to those who quit after treatment (RR = 1.3; 95% CI, 1.0–1.7) (Zevallos et al. 2009). Kuri and colleagues (2005) observed that quitting smoking decreases wound healing complications with greater effects noted for longer cessation periods (Table 6.33S). In a notable study of the potentially acutely reversible effects of smoking, Bjarnason and colleagues (2009) demonstrated that current smokers during radiotherapy have decreased inci-

dence of Grade 3+ mucositis, if treatments are delivered in the morning instead of the afternoon (42.9% vs. 76%; $p = 0.025$), suggesting that an acute break in smoking (i.e., a smoking break associated with sleeping at night) may change the toxicity associated with treatment.

Evidence Synthesis

This review is the first in the series of Surgeon General's reports to address the associations between cigarette smoking and adverse health outcomes specifically in cancer patients and survivors. Within this focus on the adverse health effects of smoking among cancer patients and survivors, evidence was summarized on the associations of cigarette smoking with multiple outcomes including all-cause and cancer-specific mortality, risk of second cancer primaries, cancer recurrence, response to cancer treatment, and treatment-related toxicities. The body of evidence was substantial, including 159 studies on all-cause mortality, 62 studies on overall survival, 52 studies on cancer-specific mortality, 15 studies on cancer-specific survival, 33 on risk of second primary cancers, 51 on cancer recurrence, 18 on response to treatment, and 82 on treatment-related toxicities.

In general, the associations were not strong, reflecting their lack of specificity and the many clinical, biological, and behavioral/social factors that determine their occurrence. Additionally, reflecting the age pattern of cancer incidence, many of the studies involved older populations, among whom comorbidities and general health status are powerful determinants of outcomes that need to be considered in characterizing the consequences of smoking. Given the nonspecificity of outcomes and their multiple determinants, smoking would be anticipated to have relatively modest effects. The follow-up time in most studies was relatively brief as well, so longer-term consequences of smoking for survivors may not be fully captured.

As with investigations on other topics related to smoking and health, misclassification of smoking is of concern. Plausibly, persons with cancer and survivors may be reluctant to disclose that they are smoking and those self-reporting as former smokers may include some proportion of current smokers. In other contexts, the potential bias from such misclassification has been examined and set aside as an explanation for observed associations (USDHHS 2004); in studies of cancer outcomes, the benefits of cessation would be reduced if the category of self-reported former smokers includes current smokers as well. Additionally, a substantial number of the studies listed in the evidence tables included former smokers in

the referent category of nonsmokers, rather than having a category of never smokers alone. If the mechanism(s) underlying the effects of smoking on outcomes are long-term, then a referent category of nonsmokers will lead to an underestimation of effect, compared to what would have been observed with a referent category comprised solely of never smokers. Further, all but one study (Marin et al. 2008) included in this review relied on self-reported smoking, and the results of that study, which used serum concentrations of cotinine to assess smoking status, suggested that relying on self-reported smoking underestimated the true association. Marin and colleagues (2008) observed that biochemically measured smoking, but not self-reported smoking, was significantly associated with wound complications.

As this is the first review in the Surgeon General's reports on associations of cigarette smoking with adverse health outcomes in cancer patients and survivors, the totality of the evidence is reviewed with reference to the key criteria for causation (USDHEW 1964; USDHHS 2004).

One essential criterion is temporality, that is, smoking needs to be antecedent to the health outcome of interest. All studies were prospective in that the active cigarette smoking occurred, and was assessed before the observation for adverse health outcomes.

Consistency is also critical. For each outcome, there was substantial evidence spanning different populations and types of cancer. Yet, most studies found smoking to have adverse consequences for cancer patients and survivors. The diversity of study populations is striking because not only were these studies carried out in different study locations by many different investigators but the study populations themselves were comprised of cancer patients and survivors who had been diagnosed with a broad spectrum of heterogeneous malignancies. In addition, patients were treated with a wide variety of cancer treatments such as surgery, chemotherapy, radiotherapy, or other anti-cancer agents. This general consistency strengthens the inference that cigarette smoking is causally associated with the overall construct of adverse health outcomes and is not just one or a few of the component endpoints used to define this construct.

In assessing evidence for causation, the strength of association is useful for considering the possibility that bias led to the observed associations. For all-cause mortality, confounding is a potential concern, as smokers may differ from nonsmokers in characteristics that affect risk of dying, such as problem drinking. For this outcome, the observed association in cancer patients and survivors is comparable to that observed in the general population (see Chapter 11). Cancer patients and survivors tend to

be older than the general population, so evidence specific to elderly populations is particularly relevant. A systematic review of smoking and all-cause mortality in people 60 years of age or older estimated a summary RR across studies of 1.83 (95% CI, 1.65–2.03) for current smoking and 1.34 (95% CI, 1.28–1.40) for former smoking (Gellert et al. 2012). Against this backdrop, the evidence for the association between cigarette smoking and all-cause mortality in cancer patients and survivors largely replicates studies in the general population. Compared to never smokers, the median RR was 1.51 for current smokers and 1.22 for former smokers. Studies that assessed dose-response provided evidence that in cancer patients and survivors the risk of dying from any cause increased as the amount smoked increased. The complementary evidence from studies that used overall survival, rather than all-cause mortality, as the endpoint was congruent with these findings. In summary, the evidence is coherent in showing a strong association between cigarette smoking and all-cause mortality/overall survival.

The evidence for cancer-specific mortality as an endpoint also showed a strong, consistent association between current smoking and cancer-specific mortality (median RR = 1.61). But, unlike the other adverse health outcomes considered, the association with former versus never smoking was null (median RR = 1.03); and a dose-response gradient between amount smoked and death from cancer was less consistently observed in this group of studies.

The risk of second primary cancers was consistently increased in smokers, with strong associations present in both current (median RR = 2.20) and former (median RR = 1.20) smokers, compared to never smokers. Strong dose-response trends by number of cigarettes smoked were observed.

The risk of cancer recurrence was consistently elevated in smokers compared to nonsmokers, with stronger associations observed in current smokers than in former smokers. Compared to never smokers, the median RR was 1.15 in former smokers and 1.42 in current smokers. Dose-response trends were observed in the majority of studies and the results of one study indicated that smoking cessation was associated with decreased risk of recurrence. Cigarette smoking was also consistently strongly associated with poorer response to treatment, with evidence of a dose-response trend of worse response with more extensive smoking.

The discussion above has addressed the specific adverse health outcomes. When this entire body of evidence is viewed collectively, there is a consistent and coherent pattern of findings showing that cigarette smoking adversely affects cancer patients throughout their course of treatment and elevates risk for future sec-

ond primary cancers and mortality. Compared to never smokers, the associations are consistently strongest in current smokers, with the associations in former smokers intermediate between current smokers and never smokers. The observed associations were strong, and the magnitude of these associations is even more impressive when one considers the methodologic issues discussed above that would tend to bias these associations toward nonsignificance.

A critical question for assessing whether cigarette smoking is a cause of adverse health outcomes in cancer patients is: Among cancer patients who are current smokers at diagnosis, what is the impact of smoking cessation compared to remaining a smoker? For each of the adverse health outcomes considered, the RRs were weaker for former versus never smokers compared to current versus never smokers. This pattern provides further evidence that removal of the exposure reduces the risk. The studies that provide direct evidence on risks following cessation consistently indicate that, compared to persistent smoking, smoking cessation leads to decreased mortality/improved survival, reduced risk of recurrence, and fewer treatment-associated toxicities. Despite the relatively small size of the evidence-base on cessation, the findings clearly bolster the evidence in favor of a causal association of smoking with adverse outcomes following cancer diagnosis.

With regard to specificity, this criterion has applicability to risk for second primary cancers. In cancer survivors, the increased risk for second primary cancers is greater for those sites for which smoking is a known causal risk factor, compared with the risk for any second primary. This specificity supports the role of smoking in increasing the risk of second cancers among survivors.

The causal criterion of coherence weighed heavily in evaluating the overall body of evidence as to whether cigarette smoking causes adverse health outcomes in cancer patients. There is already an enormous body of evidence on smoking and adverse health effects, which applies to people who have developed cancer and those who have survived following a diagnosis of cancer. Previous Surgeon General's reports have conclusively established that cigarette smoking causes increased all-cause mortality in the general population and, consequently, cigarette smoking would be expected to increase all-cause mortality in cancer patients. Similarly, active cigarette smoking is causally associated with many different types of cancer, so it would be expected a priori that cigarette smoking in cancer patients would be associated with increased risk of developing a second primary cancer known to be caused by cigarette smoking. Thus, the findings reviewed in this section are fully coherent with the general findings on smoking and health.

The preponderance of the evidence on the various outcomes considered indicates that in cancer patients, cigarette smoking is causally associated with increased mortality (i.e., poorer survival) from all-causes, cancer-specific mortality, and second primary cancers. The causality of these associations is fully coherent with the broader body of evidence on smoking and health in the population at large.

In cancer patients, the evidence also indicates that cigarette smoking is a risk factor for recurrence, poorer response to treatment, and increased treatment-related toxicity. The evidence prospectively links smoking to these outcomes. The evidence for each of these outcomes is quite consistent across diverse study populations and measurement approaches.

Conclusions

1. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and adverse health outcomes. Quitting smoking improves the prognosis of cancer patients.
2. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased all-cause mortality and cancer-specific mortality.
3. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased risk for second primary cancers known to be caused by cigarette smoking, such as lung cancer.
4. In cancer patients and survivors, the evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and (1) the risk of recurrence, (2) poorer response to treatment, and (3) increased treatment-related toxicity.

Implications

The evidence summarized in this section documents that cigarette smoking has a profound adverse impact on health outcomes in cancer patients. Considered in the context of current knowledge of the adverse health effects of cigarette smoking in the general population, it is not

surprising that cigarette smoking causes adverse health outcomes in cancer patients and survivors. This evidence has clear clinical implications. A cancer patient who is a current cigarette smoker can improve his/her prognosis by quitting smoking at any time. Evidence-based smoking cessation services for cancer patients are likely to have substantial benefits for survival. The evidence reviewed suggests, for example, that risk of dying could be lowered by 30–40% by quitting smoking at the time of diagnosis. For some cancer diagnoses, the benefit of smoking cessation may be equal to, or even exceed, the value of state-of-the-art cancer therapies (Toll et al. 2013). Evidence-based approaches are needed to assure that all cancer patients who smoke are offered effective cessation programs. The American Association of Cancer Research (Toll et al. 2013) and the American Society of Clinical Oncology (Hanna et al. 2013) have recently provided comprehensive recommendations on smoking cessation for cancer patients.

For cancer patients who remain current smokers, current smoking status is a powerful clinical risk indicator that merits the full attention of the health care team and the patient. There are a variety of smoking cessation approaches of proven efficacy, although they have not been specifically tailored to the particular context of the postdiagnosis cancer patient. The potential for increased complications and an altered response to treatment merits emphasis in patient interactions. Although research is needed to enhance the efficacy of approaches to smoking cessation for cancer patients, there is already a compelling rationale for assuring that smoking is addressed using approaches of proven efficacy. There is an evident need for a strategic research agenda to optimize cessation approaches for the particular context of the cancer patient. Effective strategies for patient education should be integral. With regard to treatment of cancer patients who smoke, the evidence reviewed has clinical implications that lead to several questions: (1) Do the optimal approaches to treat cancer differ in patients who are current smokers compared to those who do not smoke? (2) Is it better to make smoking cessation an initial priority before implementing the patient's cancer treatment regimen? Unfortunately, smoking both causes cancer and complicates its course. The evidence considered here, the first time that the topic of smoking and cancer outcomes has been addressed in the Surgeon General's reports, points to yet another avoidable set of adverse outcomes of smoking. Aggressive steps need to be taken to reduce an avoidable burden of morbidity and premature mortality in the at-risk population of cancer patients and survivors.

Evidence Summary

This extensive chapter covers a wide range of evidence on tobacco and cancer. It returns to the topic of smoking and lung cancer, which was the primary focus of the 1964 report. The section on lung cancer describes changes in cigarettes and cigarette smoke, since the first report, and tracks the changes in the types of lung cancer over time. The composition of cigarette smoke has changed to have a greater concentration of tobacco-specific nitrosamines and lower concentration of PAHs. These and other changes in cigarette smoke may have led to the rise of adenocarcinoma of the lung; the changes in composition of tobacco smoke may have implications for other cancers and, possibly, other smoking-caused diseases. The evidence reviewed shows that the risk of lung cancer associated with smoking has increased over time and during the same time period machine-measured yields of tar and nicotine have decreased.

Since the 1964 report, many additional types of cancer have been found to be causally associated with smoking. This report finds the evidence to be sufficient to infer that smoking causes liver cancer and cancer of the colon and rectum. In the 2004 report, the strength of evidence was considered to be “suggestive but not sufficient to infer a causal relationship” for both of these cancers; however, additional studies have sufficiently strengthened the evidence to infer a causal relationship between smoking and liver cancer and cancer of the colon or rectum. For liver cancer, there are several potential confounding factors, including alcohol consumption and infection with hepatitis B virus and hepatitis C virus. The review in this chapter shows that confounding can be set aside as the explanation for the association of smoking with liver cancer. With regard to colorectal cancer, the evidence has emerged in more recent decades linking smoking with this cancer. The epidemiologic studies indicate that the risk is manifest only after an exposure of long duration and, consequently, only recently have epidemiologic studies identified the association of smoking with colorectal cancer.

The association between smoking and breast cancer received detailed consideration in both the 2004 and 2006 reports of the Surgeon General. Substantial new evidence has been reported during the decade following the release of these reports. This report provides a detailed synthesis of the literature on both active smoking and exposure to secondhand smoke. The evidence shows that carcinogens in tobacco smoke do reach the tissues of the breast and active smoking affects sex hormones, which are relevant to breast cancer risk in women, in complicated ways. There are many epidemiologic studies of both active smoking and exposure to secondhand smoke; they are subject to potential bias from the reporting of smoking and exposure to secondhand smoke, and confounding is also a concern. Overall, meta-analysis finds the associations of active smoking and exposure to secondhand smoke with breast cancer risk to be weak, and the evidence was judged to be suggestive that smoking causes breast cancer.

For prostate cancer, the evidence did not show an association of smoking with incidence. The evidence confirmed the association of smoking with higher mortality from prostate cancer and also indicated that smoking may enhance progression. The biological processes underlying the suggestive association between cigarette smoking and prostate cancer mortality, case fatality, and, more seriously, unfavorable pathologic characteristics of the tumor require further investigation, particularly because incidence is not associated with smoking.

This chapter includes a new topic related to smoking and cancer, which bridges across all types of cancer—the impact of smoking on the outcome of cancer. The extensive review, included in this chapter, shows that smoking does adversely affect outcome for those developing cancer. The implications of this finding are clear: patients who develop cancer and who are still smoking need to quit. A cancer patient, who is a current cigarette smoker, can improve his/her prognosis by quitting smoking at any time. Evidence-based smoking cessation services for cancer patients are likely to have substantial benefits for survival.

Chapter Conclusions

Lung Cancer

1. The evidence is sufficient to conclude that the risk of developing adenocarcinoma of the lung from cigarette smoking has increased since the 1960s.
2. The evidence is sufficient to conclude that the increased risk of adenocarcinoma of the lung in smokers results from changes in the design and composition of cigarettes since the 1950s.
3. The evidence is not sufficient to specify which design changes are responsible for the increased risk of adenocarcinoma, but there is suggestive evidence that ventilated filters and increased levels of tobacco-specific nitrosamines have played a role.
4. The evidence shows that the decline of squamous cell carcinoma follows the trend of declining smoking prevalence.

Liver Cancer

1. The evidence is sufficient to infer a causal relationship between smoking and hepatocellular carcinoma.

Colorectal Cancer

1. The evidence is sufficient to infer a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer.

Prostate Cancer

1. The evidence is suggestive of no causal relationship between smoking and the risk of incident prostate cancer.
2. The evidence is suggestive of a higher risk of death from prostate cancer in smokers than in nonsmokers.
3. In men who have prostate cancer, the evidence is suggestive of a higher risk of advanced-stage disease and less-well-differentiated cancer in smokers than in

nonsmokers, and—independent of stage and histologic grade—a higher risk of disease progression.

Breast Cancer

1. The evidence is sufficient to identify mechanisms by which cigarette smoking may cause breast cancer.
2. The evidence is suggestive but not sufficient to infer a causal relationship between tobacco smoke and breast cancer.
3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer.
4. The evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer.

Adverse Health Outcomes in Cancer Patients and Survivors

1. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and adverse health outcomes. Quitting smoking improves the prognosis of cancer patients.
2. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased all-cause mortality and cancer-specific mortality.
3. In cancer patients and survivors, the evidence is sufficient to infer a causal relationship between cigarette smoking and increased risk for second primary cancers known to be caused by cigarette smoking, such as lung cancer.
4. In cancer patients and survivors, the evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and (1) the risk of recurrence, (2) poorer response to treatment, and (3) increased treatment-related toxicity.

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Appended Data Table for Figure 6.7

Constituent	Australian cigarettes (mean ratio)	All Canadian brands (mean ratio)	Canadian brands minus those with high nitrosamine levels (mean ratio)
Carbon monoxide	0.710400158	0.777449045	0.817811121
Ammonia	0.51269294	0.59796073	0.566238632
1-Aminonaphthalene	0.579564329	0.665667404	0.614506152
2-Aminonaphthalene	0.590445816	0.962835802	0.962683308
3-Aminobiphenyl	0.525365264	0.633630955	0.590666048
4-Aminobiphenyl	0.522789273	0.798103748	0.776117764
Benzo[a]pyrene	0.980585517	1.164614574	1.234927716
Formaldehyde	1.462076653	1.883862909	2.024465121
Acetaldehyde	0.790774813	0.81519355	0.801937805
Acetone	0.710931913	0.804254018	0.792320326
Acrolein	0.873514538	1.055653336	1.071304063
Propionaldehyde	0.764124697	0.799891575	0.787214724
Crotonaldehyde	0.69829044	1.052097525	1.061305638
Butyraldehyde	0.761127995	0.751470171	0.737407769
Hydrogen cyanide	0.88379734	1.07831255	1.00712086
Mercury	0.741893363	0.855826429	0.836552706
Lead	0.516883748	0.796979939	0.864985319
Cadmium	0.756869227	1.480584253	1.482763826
Nitric oxide	0.431633687	0.453708248	0.349412044
NOx	0.430373867	0.447235391	0.343985547
NNN	0.189049058	0.395874325	0.216319658
NNK	0.39036299	0.80005713	0.720591225
N nitrosoanatabine	0.378315716	0.378661489	0.369640472
N nitrosoanabasine	0.458034812	0.654317302	0.236635881
Pyridine	0.688916673	0.769058306	0.735334105
Quinoline	0.809029158	1.086954987	1.067824242
Hydroquinone	1.08506923	1.16636303	1.19005359
Resorcinol	1.263001552	1.239527142	1.269950615
Catechol	1.02631406	1.543078972	1.575623688
Phenol	1.00065782	1.607645714	1.605486159
m-+p-Cresol	0.929436993	1.367013458	1.348916429
o-Cresol	0.91163895	1.427291472	1.416454834
1,3 Butadiene	0.835073844	0.787929482	0.779409733
Isoprene	0.790517943	0.628854317	0.607039337
Acrylonitrile	0.711987746	0.814724264	0.798543675
Benzene	0.881502879	1.042667139	1.038655292
Toluene	0.748154731	1.006233607	1.022765635
Styrene	0.738534981	0.90339595	0.810247399
Methyl ethyl ketone	0.711908704	—	—

Sources: Counts et al. 2005; World Health Organization 2008. Reprinted with permission from World Health Organization, © 2008.
 Note: **NNK** = 4-(methylnitrosamino)-1-(3pyridyl)-1-butanone; **NNN** = N'-nitrosornornicotine; **NOx** = nitrogen oxides.

Appended Data Table for Figure 6.14

A1. Squamous cell carcinoma of the lung, males (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	46.64	25.13	23.63	—	26.08	15.98	9.84	10.80	54.28	48.52	—	17.28	—	—
1984.5	48.02	23.48	24.45	21.04	24.79	14.48	11.87	10.22	49.80	45.94	25.99	20.97	25.75	32.17
1987.5	41.21	22.19	22.83	19.04	22.30	14.59	8.03	9.01	44.93	43.98	30.14	24.21	24.98	30.69
1990.5	39.17	20.54	19.87	17.39	20.12	13.32	10.07	8.94	45.81	34.54	28.80	20.84	21.33	30.95
1993.5	34.03	18.85	18.16	14.96	18.59	14.27	7.45	8.46	36.45	31.62	29.40	24.66	17.43	28.60
1996	—	—	—	—	—	—	—	—	—	—	—	—	17.61	—
1996.5	31.36	15.84	16.49	12.97	17.42	12.75	12.56	6.87	32.94	30.14	29.52	24.87	—	25.16

A2. Squamous cell carcinoma of the lung, females (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	7.79	5.45	4.69	—	4.33	1.88	3.84	1.77	1.63	2.02	—	0.76	—	—
1984.5	9.32	6.13	5.66	2.92	5.02	1.84	3.86	2.07	2.13	2.17	1.24	0.99	2.58	1.06
1987.5	9.40	6.50	6.17	3.37	5.20	2.35	5.39	1.99	2.64	1.92	1.15	0.79	2.43	1.47
1990.5	10.56	6.65	6.26	2.95	5.55	2.94	4.26	2.10	2.64	1.93	1.49	0.37	2.14	1.84
1993.5	9.82	6.66	6.23	3.40	5.98	2.67	5.48	2.44	3.57	1.89	1.69	0.75	2.96	1.34
1996	—	—	—	—	—	—	—	—	—	—	—	—	1.96	—
1996.5	9.35	6.74	6.49	3.45	5.85	3.67	5.70	2.34	3.09	2.56	1.82	0.86	—	1.52

Appended Data Table for Figure 6.14 Continued

B1. Small cell carcinoma of the lung, males (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	14.16	12.23	11.79	13.01	7.73	7.73	7.73	—	17.06	12.36	—	7.75	—	—
1984.5	13.70	12.38	10.66	13.70	7.53	7.53	8.01	—	16.20	13.94	12.29	7.32	11.89	8.78
1987.5	14.50	12.30	10.95	12.64	8.36	8.36	9.48	4.78	14.93	15.00	11.81	9.06	10.75	8.30
1990.5	13.05	11.89	9.96	11.59	8.70	8.70	9.16	4.98	16.62	14.19	13.14	10.81	9.15	10.03
1993.5	11.54	10.57	8.69	11.54	8.46	8.46	8.33	4.12	14.67	12.68	13.04	9.08	7.62	8.78
1996	—	—	—	—	—	—	—	—	—	—	—	—	8.28	—
1996.5	10.22	10.03	8.39	10.31	8.40	8.40	6.79	3.64	13.55	12.93	12.31	10.33	—	8.16

B2. Small cell carcinoma of the lung, females (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	4.20	5.76	4.57	4.15	2.11	2.11	5.79	—	1.40	0.83	—	0.50	—	—
1984.5	5.52	6.59	5.35	5.64	2.32	2.32	4.89	—	1.28	1.90	1.73	0.27	1.86	0.70
1987.5	6.12	7.53	5.96	6.29	2.97	2.97	6.07	2.13	2.42	1.42	1.82	0.22	2.53	0.91
1990.5	7.23	7.94	6.33	6.77	3.95	3.95	5.79	2.21	3.56	1.52	2.05	0.36	2.51	1.11
1993.5	6.71	7.73	6.34	6.84	4.41	4.41	5.49	2.50	3.59	1.95	1.93	0.35	2.71	1.17
1996	—	—	—	—	—	—	—	—	—	—	—	—	2.48	—
1996.5	5.51	7.74	6.26	7.14	4.87	4.87	7.08	2.52	4.58	1.45	1.98	0.23	—	1.23

Appended Data Table for Figure 6.14 Continued
C1. Adenocarcinoma of the lung, males (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	27.26	18.47	13.85	—	11.58	7.27	7.85	4.81	9.15	13.81	—	4.15	—	—
1984.5	31.62	19.24	16.05	11.43	13.66	7.83	12.67	5.31	12.35	16.55	9.44	6.54	13.10	7.53
1987.5	32.54	20.59	16.56	11.57	15.39	9.14	11.21	6.09	14.97	20.27	9.18	5.05	12.59	9.37
1990.5	30.86	21.21	15.53	11.73	14.21	10.16	11.80	5.95	12.58	21.67	12.59	6.85	11.90	9.92
1993.5	34.99	21.81	15.77	11.40	14.86	10.62	10.79	6.04	13.13	23.01	11.82	8.17	12.65	11.59
1996	—	—	—	—	—	—	—	—	—	—	—	—	13.32	—
1996.5	32.32	20.77	15.56	11.17	15.29	11.03	12.62	5.95	13.92	21.23	13.38	8.12	—	13.85

C2. Adenocarcinoma of the lung, males (rate per 100,000 person-years)

Year	United States (Blacks)	United States (Whites)	Canada	Australia (New South Wales)	Denmark	Norway	Iceland	Sweden	Netherlands (Eindhoven)	Italy (Varese)	Slovenia	Spain	Switzerland	France
1981.5	11.37	10.53	7.75	—	7.02	3.04	8.50	2.92	2.07	2.55	—	1.59	—	—
1984.5	12.81	11.93	10.06	3.70	8.57	3.79	12.95	3.30	2.17	3.14	3.27	1.30	4.26	1.53
1987.5	14.54	13.19	11.12	4.86	10.55	4.32	14.22	3.89	3.08	3.60	3.25	1.87	4.58	1.70
1990.5	15.64	14.60	11.33	5.10	10.61	4.98	12.80	4.27	3.51	3.77	4.20	1.94	4.94	2.03
1993.5	16.68	15.73	12.34	5.23	12.21	6.31	16.23	4.79	4.01	5.44	3.78	2.15	5.71	2.71
1996	—	—	—	—	—	—	—	—	—	—	—	—	5.92	—
1996.5	16.97	15.73	13.52	5.95	13.68	6.69	10.58	5.11	4.08	5.48	5.10	2.86	—	3.26

Source: Devesa et al. 2005. Reprinted with permission from John Wiley & Sons, Inc., © 2005.
 Note: Incidence rates were calculated for 3-year time periods: 1980–1982 (plotted at 1981.5), 1983–1985 (plotted at 1984.5), 1986–1988 (plotted at 1987.5), 1989–1991 (plotted at 1990.5), 1992–1994 (plotted at 1993.5), 1996 (Switzerland only; plotted at 1996), and 1995–1997 (plotted at 1996.5). Incidence rates were age-adjusted by the direct method, using the Segi world standard (Bray et al. 2002), and expressed per 100,000 person-years.

Appended Data Table for Figure 6.17

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Austin and Cole 1986	Case-control	United States	All	1.6 (0.7–3.7)	1.56
LaVecchia et al. 1988	Case-control	Italy	All	0.9 (0.6–1.5)	2.84
Tsukuma et al. 1990	Case-control	Japan	All	2.5 (1.4–4.5)	2.45
Choi and Kahyo 1991	Case-control	Korea	Males	1.0 (0.7–1.6)	3.44
Tanaka et al. 1992	Case-control	Japan	All	1.5 (0.8–2.7)	2.34
Takeshita et al. 2000	Case-control	Japan	Males	1.6 (0.7–3.5)	1.64
Hassan et al. 2002	Case-control	United States	All	1.2 (0.6–2.4)	2.00
Farker et al. 2003	Case-control	Germany	All	2.4 (0.9–6.4)	1.20
Marrero et al. 2005	Case-control	United States	All	10.9 (3.5–34.0)	0.96
Franceschi et al. 2006	Case-control	Italy	All	1.1 (0.6–2.2)	2.25
Zhu et al. 2007	Case-control	United States	Males	1.5 (0.8–2.7)	2.44
Hara et al. 2008	Case-control	Japan	All	1.8 (0.6–5.1)	1.07
Case control: Subtotal (I-squared = 53.0%, p = 0.015)				1.6 (1.2–2.1)	24.20
Hirayama 1989	Cohort	Japan	Males	3.1 (1.8–5.4)	2.64
Akiba and Hirayama 1990	Cohort	Japan	Males	1.5 (1.2–1.9)	4.59
Akiba and Hirayama 1990	Cohort	Japan	Females	1.6 (1.2–2.0)	4.43
Hsing et al. 1990	Cohort	United States	Males	2.4 (1.6–3.5)	3.52
Shibata et al. 1990	Cohort	Japan	Males, Cohort I	1.1 (0.2–4.7)	0.55
Shibata et al. 1990	Cohort	Japan	Males, Cohort II	3.6 (0.6–22.3)	0.43
Goodman et al. 1994	Cohort	Japan	All	2.2 (1.5–3.2)	3.54
McLaughlin et al. 1995	Cohort	United States	Males	1.8 (1.4–2.3)	4.47
Nordlund et al. 1997	Cohort	Sweden	Females	0.7 (0.2–2.0)	1.06
Mizoue et al. 2000	Cohort	Japan	Males	3.3 (1.2–9.5)	1.12
Evans et al. 2002	Cohort	China	Males	0.9 (0.8–1.1)	5.01
Evans et al. 2002	Cohort	China	Females	2.0 (0.9–4.2)	1.74
Jee et al. 2004	Cohort	Korea	Males	1.5 (1.3–1.7)	5.13
Jee et al. 2004	Cohort	Korea	Females	1.1 (0.8–1.7)	3.61
Ogimoto et al. 2004	Cohort	Japan	Males, 40–59 years of age	2.0 (0.8–5.1)	1.26
Ogimoto et al. 2004	Cohort	Japan	Males, 60–69 years of age	2.6 (1.2–5.8)	1.65
Ogimoto et al. 2004	Cohort	Japan	Females, 40–59 years of age	2.8 (0.6–13.1)	0.58
Ogimoto et al. 2004	Cohort	Japan	Females, 60–69 years of age	1.5 (0.5–4.9)	0.91
Wen et al. 2004	Cohort	China	Males	1.5 (1.2–1.8)	4.68
Wen et al. 2004	Cohort	China	Females	5.0 (2.4–10.7)	1.79
Yun et al. 2005	Cohort	Korea	Males	1.5 (1.3–1.7)	5.06
Fujita et al. 2006	Cohort	Japan	Anti-HCV positive	9.6 (1.5–61.4)	0.41
Fujita et al. 2006	Cohort	Japan	Anti-HCV negative	1.7 (0.6–5.1)	1.04

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Chen et al. 2008	Cohort	China	HBV negative and HCV negative	2.4 (1.2–5.0)	1.88
Chen et al. 2008	Cohort	China	HBV positive and HCV negative	1.1 (0.8–1.5)	4.03
Chen et al. 2008	Cohort	China	HBV negative and HCV positive	1.4 (0.6–3.3)	1.51
Ohishi et al. 2008	Cohort	Japan	All	2.0 (0.8–5.0)	1.39
Koh et al. 2011	Cohort	Singapore	All	1.6 (1.3–2.1)	4.45
Trichopoulos et al. 2011	Cohort	Europe	All	4.6 (1.9–10.9)	1.46
Oh et al. 2012	Cohort	Korea	All	1.3 (0.6–2.6)	1.86
Cohort: Subtotal (I-squared = 69.6%, p = 0.000)				1.7 (1.5–1.9)	75.80
Overall (I-squared = 65.5%, p = 0.000)				1.7 (1.5–1.9)	100.00

Notes: Weights are from random effects analysis. **CI** = confidence interval; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus.

Appended Data Table for Figure 6.18

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
LaVecchia et al. 1988	Case-control	Italy	All	0.9 (0.6–1.5)	11.29
Choi and Kahyo 1991	Case-control	Korea	Males	1.0 (0.7–1.6)	13.88
Tanaka et al. 1992	Case-control	Japan	All	1.5 (0.8–2.7)	9.18
Hassan et al. 2002	Case-control	United States	All	1.2 (0.6–2.4)	7.78
Hara et al. 2008	Case-control	Japan	All	1.8 (0.6–5.1)	4.05
Ohishi et al. 2008	Case-control	Japan	All	2.0 (0.8–5.0)	5.32
Case-control: Subtotal (I-squared = 0.0%, p = 0.549)				1.2 (0.9–1.5)	51.50
Liaw and Chen 1998	Cohort	China	Males	2.2 (1.4–3.6)	12.09
Jee et al. 2004	Cohort	Korea	Males	1.5 (1.3–1.7)	21.66
Fujita et al. 2006	Cohort	Japan	Anti-HCV positive	9.6 (1.5–61.4)	1.52
Fujita et al. 2006	Cohort	Japan	Anti-HCV negative	1.7 (0.6–5.1)	3.96
Koh et al. 2011	Cohort	Singapore	HBV negative and HCV negative	1.8 (0.6–5.7)	3.69
Trichopoulos et al. 2011	Cohort	Europe	All	4.6 (1.9–10.9)	5.58
Cohort: Subtotal (I-squared = 57.5%, p = 0.038)				2.2 (1.4–3.3)	48.50
Overall (I-squared = 47.1%, p = 0.036)				1.6 (1.2–2.0)	100.00

Note: Weights are from random effects analysis. **CI** = confidence interval; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus.

Appended Data Table for Figure 6.19

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Lam et al. 1982	Case-control	China	All	1.3 (0.7–2.4)	2.46
Stemhagan et al. 1983	Case-control	United States	Males	0.7 (0.5–1.1)	3.91
Stemhagan et al. 1983	Case-control	United States	Females	1.0 (0.6–1.7)	2.76
Austin et al. 1986	Case-control	United States	All	1.1 (0.5–2.4)	1.62
Lu et al. 1988	Case-control	China	All	1.1 (0.7–1.8)	3.60
Kew et al. 1990	Case-control	South Africa	Black females	2.2 (0.8–6.1)	1.04
Olubuyide and Bamgboye 1990	Case-control	Nigeria	All	1.7 (0.9–3.1)	2.34
Lin et al. 1991	Case-control	China	Males, HBsAg negative, alcoholic cirrhosis	0.6 (0.4–1.0)	4.18
Ross et al. 1992	Case-control	China	Males	1.8 (0.6–5.6)	0.88
Goritsas et al. 1995	Case-control	Greece	All	1.6 (0.9–2.0)	4.05
Siemiatycki et al. 1995	Case-control	Canada	Males, 35–70 years of age	0.9 (0.4–2.1)	1.47
Koide et al. 2000	Case-control	Japan	All	5.4 (1.1–26.7)	0.45
Lam et al. 2001	Case-control	China	Males, 35–69 years of age	1.6 (1.3–1.9)	6.81
Lam et al. 2001	Case-control	China	Males, 70 years of age and older	1.2 (0.9–1.5)	6.07
Lam et al. 2001	Case-control	China	Females, 35–69 years of age	1.4 (0.8–2.4)	2.99
Lam et al. 2001	Case-control	China	Females, 70 years of age and older	1.4 (0.9–2.0)	4.16
Yu et al. 2002	Case-control	China	All	0.7 (0.3–1.7)	1.31
Munaka et al. 2003	Case-control	Japan	All	1.2 (0.6–2.7)	1.63
Marrero et al. 2005	Case-control	United States	All	12.3 (4.4–34.2)	1.02
Hassan et al. 2009	Case-control	United States	All	1.8 (1.3–2.4)	5.32
Jeng et al. 2009	Case-control	China	All	2.3 (1.5–3.5)	3.97
Soliman et al. 2010	Case-control	Egypt	All	1.4 (0.7–2.8)	1.98
Case-control: Subtotal (I-squared = 66.6%, p = 0.000)				1.4 (1.1–1.7)	64.02
Yu and Chen 1993	Cohort	China	Males	1.2 (0.4–3.1)	1.02
Goodman et al. 1994	Cohort	Japan	All	2.2 (1.5–3.2)	4.43
McLaughlin et al. 1995	Cohort	United States	Males	1.7 (1.3–2.2)	5.97
Chen et al. 1996	Cohort	China	All	3.6 (1.3–10.6)	0.98
Lam et al. 1997	Cohort	China	Males	1.1 (0.4–2.9)	1.08
Liu et al. 1998	Cohort	China	Males, 35–69 years of age	1.4 (1.3–1.5)	8.95
Liu et al. 1998	Cohort	China	Females, 35–69 years of age	1.2 (1.1–1.3)	8.45
Mori et al. 2000	Cohort	Japan	All	2.1 (0.6–7.2)	0.73
Wang et al. 2003	Cohort	China	Males	1.5 (1.1–2.3)	4.37
Cohort: Subtotal (I-squared = 58.9%, p = 0.013)				1.5 (1.3–1.7)	35.98
Overall (I-squared = 63.7%, p = 0.000)				1.4 (1.3–1.6)	100.00

Note: Weights are from random effects analysis. CI = confidence interval; HBsAg = hepatitis B surface antigen.

Appended Data Table for Figure 6.20

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Ross et al. 1992	Case-control	China	Males	1.8 (0.6–5.6)	4.35
Yu and Chen 1993	Case-control	China	Males	1.2 (0.4–3.1)	5.17
Goritsas et al. 1995	Case-control	Greece	All	1.6 (0.9–2.0)	32.78
Hassan et al. 2009	Case-control	United States	All	1.8 (1.3–2.4)	57.70
Subtotal: Case-control (I-squared = 0.0%, p = 0.89)				1.7 (1.4–2.2)	100.00
Overall (I-squared = 0.0%, p = 0.89)				1.7 (1.4–2.2)	100.00

Note: Weights are from random effects analysis. **CI** = confidence interval.

Appended Data Table for Figure 6.21

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
Lam et al. 1982	Case-control	China	HBsAg negative	2.9 (0.8–10.7)	5.11
Austin and Cole 1986	Case-control	United States	HBsAg negative	1.1 (0.5–2.4)	7.31
Lin et al. 1991	Case-control	China	Males, HBsAg negative, alcoholic cirrhosis negative	0.6 (0.4–1.0)	8.91
Goritsas et al. 1995	Case-control	Greece	HBsAg negative	6.1 (1.5–25.5)	4.73
Yuan et al. 2004	Case-control	United States	Blacks and Whites, HBV negative and HCV negative	1.7 (1.0–3.0)	8.33
Franceschi et al. 2006	Case-control	Italy	HBsAg negative and anti-HCV negative	1.0 (0.5–2.0)	7.88
Hassan et al. 2008	Case-control	United States	Males, HBsAg1 negative and anti-HBc13 negative	2.0 (1.2–3.3)	8.50
Hassan et al. 2008	Case-control	United States	Females, HBsAg1 negative and anti-HBc13 negative	1.1 (0.6–1.9)	8.22
Jeng et al. 2009	Case-control	China	HBsAg negative and anti-HCV negative	44.4 (17.8–116.1)	6.62
Soliman et al. 2010	Case-control	Egypt	HCV negative	0.5 (0.1–1.8)	4.94
Case-control: Subtotal (I-squared = 88.6%, p = 0.000)				1.9 (1.0–3.7)	70.55
Jee et al. 2004	Cohort	Korea	Males, HBsAg negative	1.1 (0.9–1.4)	9.39
Fujita et al. 2006	Cohort	Japan	Anti-HCV negative	1.7 (0.6–5.1)	5.99
Chen et al. 2008	Cohort	China	HBV negative and HCV negative	2.4 (1.2–5.0)	7.57
Koh et al. 2011	Cohort	China	HBsAg negative, anti-HBc negative, anti-HBs negative, and anti-HCV negative	1.6 (0.6–4.2)	6.50
Cohort: Subtotal (I-squared = 40.1%, p = 0.171)				1.5 (1.0–2.2)	29.45
Overall (I-squared = 84.7%, p = 0.000)				1.8 (1.2–2.7)	100.00

Notes: Weights are from random effects analysis. **CI** = confidence interval; **HBc13** = hepatitis B virus core 13; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus.

Appended Data Table for Figure 6.22

Study	Design	Country	Population	Effect size (95% CI)	Weight (%)
LaVecchia et al. 1988	Case-control	Italy	All	0.6 (0.4–1.0)	5.41
Tsukuma et al. 1990	Case-control	Japan	All	0.7 (0.3–1.9)	2.75
Choi and Kahyo 1991	Case-control	Korea	Males	0.6 (0.4–1.2)	4.33
Tanaka et al. 1992	Case-control	Japan	All	1.5 (0.8–2.8)	4.24
Takehita et al. 2000	Case-control	Japan	Males	0.7 (0.3–1.5)	3.26
Farker et al. 2003	Case-control	Germany	All	2.5 (1.2–5.0)	3.79
Marrero et al. 2005	Case-control	United States	All	13.3 (4.5–38.9)	2.23
Franceschi et al. 2006	Case-control	Italy	All	0.8 (0.4–1.5)	4.39
Zhu et al. 2007	Case-control	United States	Males	1.9 (1.0–3.3)	4.64
Hara et al. 2008	Case-control	Japan	All	0.8 (0.3–2.3)	2.41
Hassan et al. 2008	Case-control	United States	All	1.4 (0.9–2.1)	5.56
Case control: Subtotal (I-squared = 76.4%, p = 0.000)				1.2 (0.8–1.9)	43.12
Shibata et al. 1990	Cohort	Japan	Males, Cohort II	2.9 (0.3–29.0)	0.64
Goodman et al. 1994	Cohort	Japan	All	2.3 (1.5–3.6)	5.60
McLaughlin et al. 1995	Cohort	United States	Males	1.5 (1.2–2.0)	6.88
Mizoue et al. 2000	Cohort	Japan	All	2.9 (1.0–8.4)	2.27
Jee et al. 2004	Cohort	Korea	Males	1.1 (1.0–1.3)	7.57
Jee et al. 2004	Cohort	Korea	Females	1.3 (0.8–2.1)	5.22
Ogimoto et al. 2004	Cohort	Japan	Males, 40–59 years of age	2.4 (0.8–6.8)	2.31
Ogimoto et al. 2004	Cohort	Japan	Males, 60–69 years of age	2.7 (1.2–6.1)	3.24
Ogimoto et al. 2004	Cohort	Japan	Females, 60–69 years of age	1.2 (0.2–8.7)	0.81
Fujita et al. 2006	Cohort	Japan	Anti-HCV positive	7.8 (1.1–56.0)	0.83
Fujita et al. 2006	Cohort	Japan	Anti-HCV negative	0.3 (0.0–1.7)	1.01
Chen et al. 2008	Cohort	China	HBV negative and HCV negative	1.0 (0.2–4.6)	1.24
Chen et al. 2008	Cohort	China	HBV positive and HCV negative	1.0 (0.5–2.0)	3.84
Chen et al. 2008	Cohort	China	HBV negative and HCV positive	2.9 (0.9–9.1)	2.01
Ohishi et al. 2008	Cohort	Japan	All	1.1 (0.3–5.1)	1.33
Koh et al. 2011	Cohort	Singapore	All	1.1 (0.8–1.5)	6.47
Trichopoulos et al. 2011	Cohort	Europe	All	2.0 (0.9–4.4)	3.32
Oh et al. 2012	Cohort	Korea	All	1.2 (0.4–3.3)	2.30
Cohort: Subtotal (I-squared = 46.9%, p = 0.015)				1.5 (1.2–1.8)	56.88
Overall (I-squared = 62.7%, p = 0.000)				1.4 (1.1–1.7)	100.00

Notes: Weights are from random effects analysis. **CI** = confidence interval; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HCV** = hepatitis C virus.

Appended Data Table for Figure 6.23

Study	Type of examination	RR (95% CI)
Demers et al. 1988a	Partial endoscopy	2.19 (1.26–3.81)
Kato et al. 1990b	Partial endoscopy	0.83 (0.55–1.27)
Kato et al. 1990c	Partial endoscopy	0.75 (0.43–1.29)
Kato et al. 1990d	Partial endoscopy	1.06 (0.56–2.02)
Shahangian et al. 1991	Partial endoscopy	3.56 (0.91–13.94)
Zahm et al. 1991a	Partial endoscopy	2.70 (1.00–7.10)
Honjo et al. 1992a	Partial endoscopy	3.20 (1.74–5.91)
Kune et al. 1992a	Partial endoscopy	2.48 (1.00–6.10)
Giovannucci et al. 1994aa	Partial endoscopy	1.57 (1.16–2.14)
Giovannucci et al. 1994be	Partial endoscopy	2.06 (1.66–2.56)
Martinez et al. 1995	Partial endoscopy	2.29 (1.28–4.07)
Lubin et al. 1997	Partial endoscopy	2.40 (1.10–5.50)
Ji et al. 2006	Partial endoscopy	1.80 (1.50–2.10)
Mitrou et al. 2006	Partial endoscopy	3.37 (2.52–4.50)
Reid et al. 2006	Partial endoscopy	1.82 (1.17–2.84)
Stern et al. 2006	Partial endoscopy	2.20 (1.60–3.00)
Subtotal pooled RR: Partial endoscopy, current smokers		2.05 (1.68–2.51)
Kikendall et al. 1989	Full colonoscopy	2.79 (1.30–5.97)
Cope et al. 1991	Full colonoscopy	2.76 (1.34–5.68)
Monnet et al. 1991a	Full colonoscopy	1.90 (0.90–4.00)
Clark et al. 1993a	Full colonoscopy	1.05 (0.14–7.93)
Olsen and Kronborg 1993	Full colonoscopy	2.00 (1.10–3.50)
Nagata et al. 1999	Full colonoscopy	2.72 (2.02–3.67)
Almendingen et al. 2000	Full colonoscopy	3.80 (0.90–14.40)
Breuer-Katschinski et al. 2000	Full colonoscopy	2.30 (1.10–4.60)
Hoshiyama et al. 2000	Full colonoscopy	2.86 (1.21–6.80)
Inoue et al. 2000a	Full colonoscopy	3.59 (2.19–5.88)
Ulrich et al. 2001	Full colonoscopy	2.10 (1.50–3.10)
Cardoso et al. 2002	Full colonoscopy	1.87 (0.97–3.63)
Erhardt et al. 2002	Full colonoscopy	1.26 (0.72–2.20)
Voskuil et al. 2002	Full colonoscopy	1.71 (0.64–4.52)
Sparks et al. 2004	Full colonoscopy	1.87 (1.34–2.61)
Tiemersma et al. 2004	Full colonoscopy	2.10 (1.38–3.18)
Gong et al. 2005	Full colonoscopy	2.75 (1.76–4.29)
Larsen et al. 2006	Full colonoscopy	1.59 (1.25–2.01)
Ashktorab et al. 2007	Full colonoscopy	14.50 (2.76–76.17)
Subtotal pooled RR: Full colonoscopy, current smokers		2.22 (1.86–2.67)
Overall pooled RR: Current smokers		2.14 (1.86–2.46)

Source: Adapted from Botteri et al. 2008b, with permission from Elsevier © 2008.

Note: Partial endoscopy group is composed of studies in which some or all controls underwent partial colon examination. Full colonoscopy group is composed of studies in which all controls underwent complete colon examination. **CI** = confidence interval; **RR** = relative risk.

^aEstimates for males only.

^bEstimates for distal colon.

^cEstimates for proximal colon.

^dEstimates for rectum.

^eEstimates for women only.

Appended Data Table for Figure 6.24

Study	Type of examination	RR (95% CI)
Kato et al. 1990a	Partial endoscopy	0.93 (0.59–1.49)
Kato et al. 1990b	Partial endoscopy	1.03 (0.57–1.85)
Kato et al. 1990c	Partial endoscopy	0.95 (0.46–1.94)
Shahangian et al. 1991	Partial endoscopy	2.00 (0.56–7.09)
Zahm et al. 1991d	Partial endoscopy	1.20 (0.50–2.70)
Honjo et al. 1992d	Partial endoscopy	2.20 (1.10–4.30)
Martinez et al. 1995	Partial endoscopy	1.60 (1.03–2.49)
Lubin et al. 1997	Partial endoscopy	1.50 (1.10–2.10)
Ji et al. 2006	Partial endoscopy	1.10 (1.00–1.20)
Mitrou et al. 2006	Partial endoscopy	1.52 (1.23–1.88)
Reid et al. 2006	Partial endoscopy	1.29 (0.86–1.95)
Stern et al. 2006	Partial endoscopy	1.20 (1.00–1.60)
Subtotal pooled RR: Partial endoscopy, former smokers		1.31 (1.11–1.56)
Kikendall et al. 1989	Full colonoscopy	1.15 (0.57–2.34)
Monnet et al. 1991d	Full colonoscopy	2.70 (1.30–5.70)
Clark et al. 1993d	Full colonoscopy	0.85 (0.12–6.00)
Olsen and Kronborg 1993	Full colonoscopy	2.10 (1.10–3.90)
Nagata et al. 1999	Full colonoscopy	2.71 (1.90–3.85)
Almendingen et al. 2000	Full colonoscopy	1.40 (0.40–4.40)
Breuer-Katschinski et al. 2000	Full colonoscopy	1.00 (0.62–1.70)
Hoshiyama et al. 2000	Full colonoscopy	1.53 (0.61–3.84)
Inoue et al. 2000d	Full colonoscopy	1.10 (0.60–1.90)
Ulrich et al. 2001	Full colonoscopy	1.40 (1.00–1.90)
Cardoso et al. 2002	Full colonoscopy	2.25 (1.36–3.72)
Erhardt et al. 2002	Full colonoscopy	1.97 (1.28–3.03)
Voskuil et al. 2002	Full colonoscopy	2.00 (0.88–4.53)
Sparks et al. 2004	Full colonoscopy	1.75 (1.35–2.28)
Tiemersma et al. 2004	Full colonoscopy	1.62 (1.12–2.33)
Larsen et al. 2006	Full colonoscopy	1.06 (0.79–1.41)
Ashktorab et al. 2007	Full colonoscopy	0.66 (0.07–6.56)
Subtotal pooled RR: Full colonoscopy, former smokers		1.61 (1.37–1.89)
Overall pooled RR: Former smokers		1.47 (1.29–1.67)

Source: Adapted from Botteri et al. 2008b, with permission from Elsevier © 2008.

Note: Partial endoscopy group is composed of studies in which some or all controls underwent partial colon examination. Full colonoscopy group is composed of studies in which all controls underwent complete colon examination. **CI** = confidence interval; **RR** = relative risk.

^aEstimates for distal colon.

^bEstimates for proximal colon.

^cEstimates for rectum.

^dEstimates for males only.

Appended Data Table for Figure 6.25

Study	Number of cigarettes smoked per day	RR (95% CI)
Akiba and Hirayama 1990	1–4	3.1 (1.4–6.4)
Akiba and Hirayama 1990	5–14	1.0 (0.7–1.6)
Akiba and Hirayama 1990	15–24	0.9 (0.6–1.4)
Akiba and Hirayama 1990	25–34	0.8 (0.2–2.1)
Akiba and Hirayama 1990	35 or more	3.0 (1.0–7.1)
Hsing et al. 1990	1–19	1.6 (0.8–3.3)
Hsing et al. 1990	20–29	1.7 (0.8–3.5)
Hsing et al. 1990	30 or more	1.4 (0.4–4.4)
Hsing et al. 1991	1–9	1.1 (1.0–1.3)
Hsing et al. 1991	10–20	1.2 (1.1–1.3)
Hsing et al. 1991	21–39	1.2 (1.1–1.4)
Hsing et al. 1991	40 or more	1.5 (1.2–1.9)
Adami et al. 1996	—	1.3 (1.1–1.5)
Coughlin et al. 1996	—	1.3 (1.1–1.5)
Rodriguez et al. 1997	—	1.3 (1.2–1.6)
Lotufo et al. 2000	1–19	1.3 (0.5–3.5)
Lotufo et al. 2000	20 or more	1.2 (0.5–2.7)
Rohrmann et al. 2007 (1963 cohort)	—	2.4 (0.9–6.0)
Rohrmann et al. 2007 (1975 cohort)	—	2.2 (0.7–7.1)
Giovannucci et al. 2007	—	1.4 (1.0–1.9)
Batty et al. 2008	—	1.3 (1.0–1.7)
Watters et al. 2009	—	1.7 (1.3–2.3)
Weinmann et al. 2010	—	1.5 (1.1–2.0)

Note: Includes studies reporting a relative risk and 95% confidence interval for current smoking or current number of cigarettes smoked per day. See Table 6.8S for additional studies for which confidence intervals were not reported. **CI** = confidence interval; **RR** = relative risk.

