The Health Consequences of Smoking—50 Years of Progress

A Report of the Surgeon General

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Introduction

On January 11, 1964, Luther L. Terry, M.D., Surgeon General of the United States, released *Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service*. This report, written at the request of President John F. Kennedy, was in response to the evidence on smoking and lung cancer that had been accumulating since the 1950s (see Chapter 2, "Fifty Years of Change 1964–2014"). This was the first in the series that is now generally referred to as the Surgeon General's reports. On the basis of more than 7,000 articles in the biomedical literature relating to smoking and disease that were available at the time, the Advisory Committee concluded that cigarette smoking is:

- Associated with 70% higher all-cause mortality rates among men
- A cause of lung cancer and laryngeal cancer in men
- A probable cause of lung cancer in women
- The most important cause of chronic bronchitis (U.S. Department of Health, Education, and Welfare [USDHEW] 1964).

For several days, the report was the topic of newspaper headlines across the country and lead stories on television newscasts (Parascandola 1997). Later, it was ranked among the top news stories of the 20th century (*USA Today* 1999). The release of that report was one of the first in a series of steps, still being taken 50 years later, to diminish the impact of tobacco use on the health of people worldwide. Ever since, individual citizens, private organizations, public agencies, and elected officials have pursued the Advisory Committee's call for "appropriate remedial action."

Early on, in response to the 1964 report, the U.S. Congress passed the *Federal Cigarette Labeling and Advertising Act of 1965* and the *Public Health Cigarette Smoking Act of 1969*. These laws required a health warning on cigarette packages, banned cigarette advertising in the broadcasting media, and called for an annual report on the health consequences of smoking. Since then, there have been several actions at the federal level—the enactment of the *Family Smoking Prevention and Tobacco Control Act* in 2009, and the publication of *Ending the Tobacco Epidemic: A Tobacco Control Strategic Plan for the U.S. Department of Health and Human Services* (USDHHS 2010a).

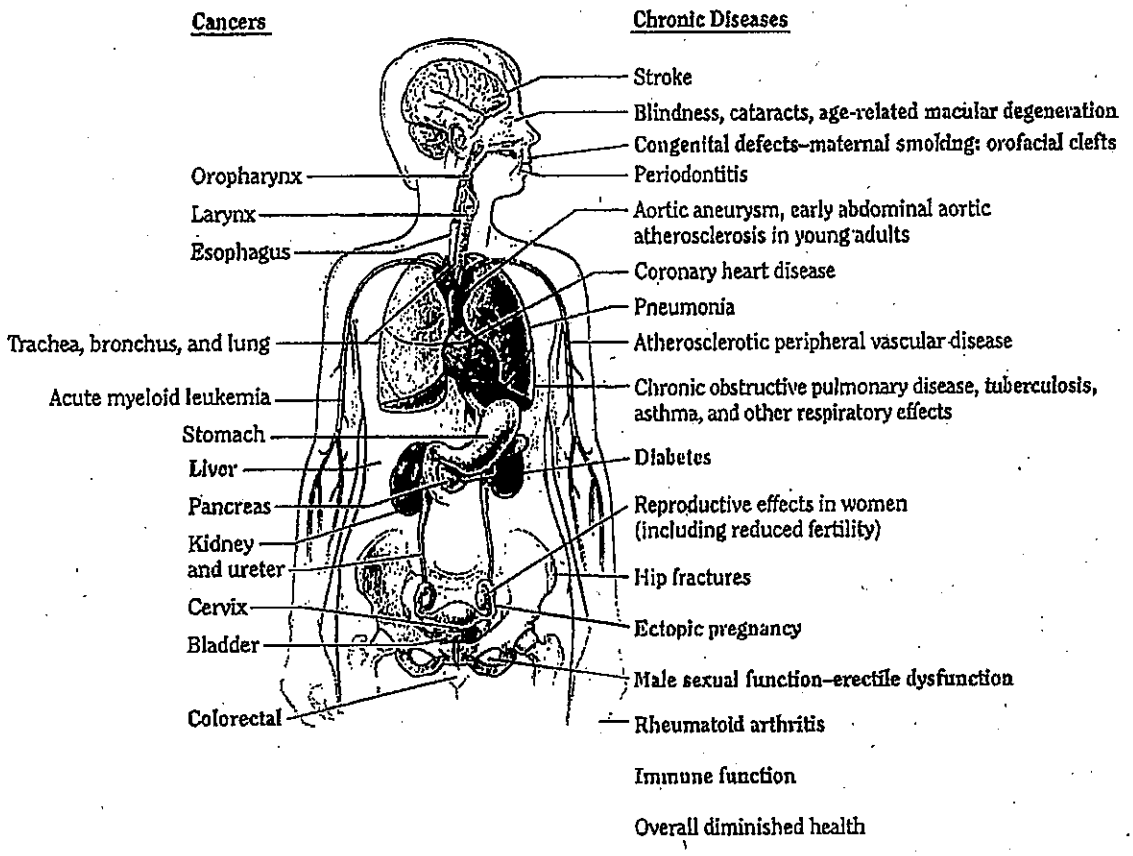
Since that first report in 1964, knowledge of the health consequences of smoking and involuntary exposure to tobacco smoke has expanded dramatically (see Chapter 4, "Advances in Knowledge on the Health Consequences of Smoking: From 1964–2014"). This series of reports has provided definitive syntheses of the evolving evidence on smoking and health. The topics have ranged widely, including comprehensive coverage of the adverse health effects of active smoking and exposure to secondhand smoke (USDHEW 1979; U.S. Department of Health and Human Services [USDHHS] 1986, 2004, 2006), the impact of tobacco control policies (USDHHS 2000), and addiction (USDHHS 1988). A goal of these reports has been to synthesize available evidence to reach conclusions on causality that have public health implications. In reaching conclusions on causation, the reports have followed a model that originated with the 1964 report: compilation of all relevant lines of scientific evidence, critical assessment of the evidence, evaluation of the strength of evidence by using guidelines for evidence evaluation, and a summary conclusion on causation (USDHEW 1964; USDHHS 2004; Table 1.1; Chapter 3, "Producing the Surgeon General's Report from 1964–2014: Process and Purpose"). The Surgeon General's reports have established a long list of health consequences and diseases caused by tobacco use and exposure to tobacco smoke (see Chapter 4). Fifty years later, this report documents that our knowledge continues to expand as new causal conclusions are still being added to that long list (Figures 1.1A and 1.1B).

Table 1.1 Four-level hierarchy for classifying the strength of causal inferences from available evidence

Level 1	Evidence is **sufficient** to infer a causal relationship
Level 2	Evidence is **suggestive but not sufficient** to infer a causal relationship
Level 3	Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting)
Level 4	Evidence is **suggestive of no causal relationship**

Source: U.S. Department of Health and Human Services 2004.

Figure 1.1A The health consequences causally linked to smoking

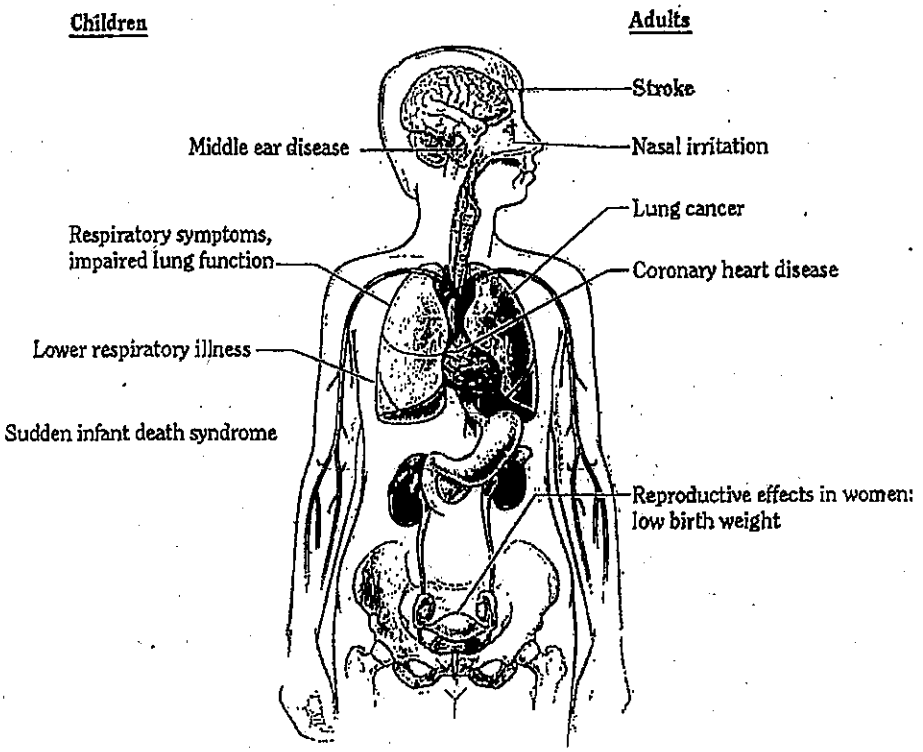


Source: USDHHS 2004, 2006, 2012.
Note: The condition in red is a new disease that has been causally linked to smoking in this report.

Organization of the Report

This report is divided into three sections. Section 1 "Historical perspective, overview, and conclusions" provides an overall summary of the report and its conclusions. It also provides a summary of the history of this series of reports, moving from their origins in 1964 to the present, contrasting what we knew in 1964 with what we know now in 2014. Section 2 "The Health Consequences of Active and Passive Smoking: The Evidence in 2014" provides a direct link to the 1964 report, which addressed the health effects of active smoking only. The first chapter in this section gives a 50-year perspective on the identification of the health consequences of active smoking and exposure to secondhand smoke. The other chapters in this section provide updates on critical topics and on topics for which the evidence has advanced, since the previous reviews in the 2004 and 2006 Surgeon General's reports, *The Health Consequences of Smoking: A Report of the Surgeon General* and *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General,* including a brief review of the state of

Figure 1.1B The health consequences causally linked to exposure to secondhand smoke



Source: USDHHS 2004, 2006.
Note: The condition in red is a new disease that has been causally linked to smoking in this report.

the evidence. Understanding of mechanisms, as laid out in the 2010 report, *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease,* is also (USDHHS 2010b). Active smoking and exposure to secondhand smoke are covered in the same chapters. Section 3 "Tracking and Ending the Epidemic" includes a descriptive chapter on the patterns of smoking, a chapter on the impact of the tobacco control environment on smoking since 1964, and additional chapters providing estimates of premature deaths that are avoidable. The final chapter "A Vision for the Ending the Tobacco Epidemic" outlines broad strategies and potential courses of action for tobacco control in the future.

Each section within the chapters on the health consequences of smoking (Chapters 6 – 11) is 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.

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-β1, 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 6.3*S* and 6.4*S*). 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 6.3*S*) and 54 cohort studies (Table 6.4*S*)—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.

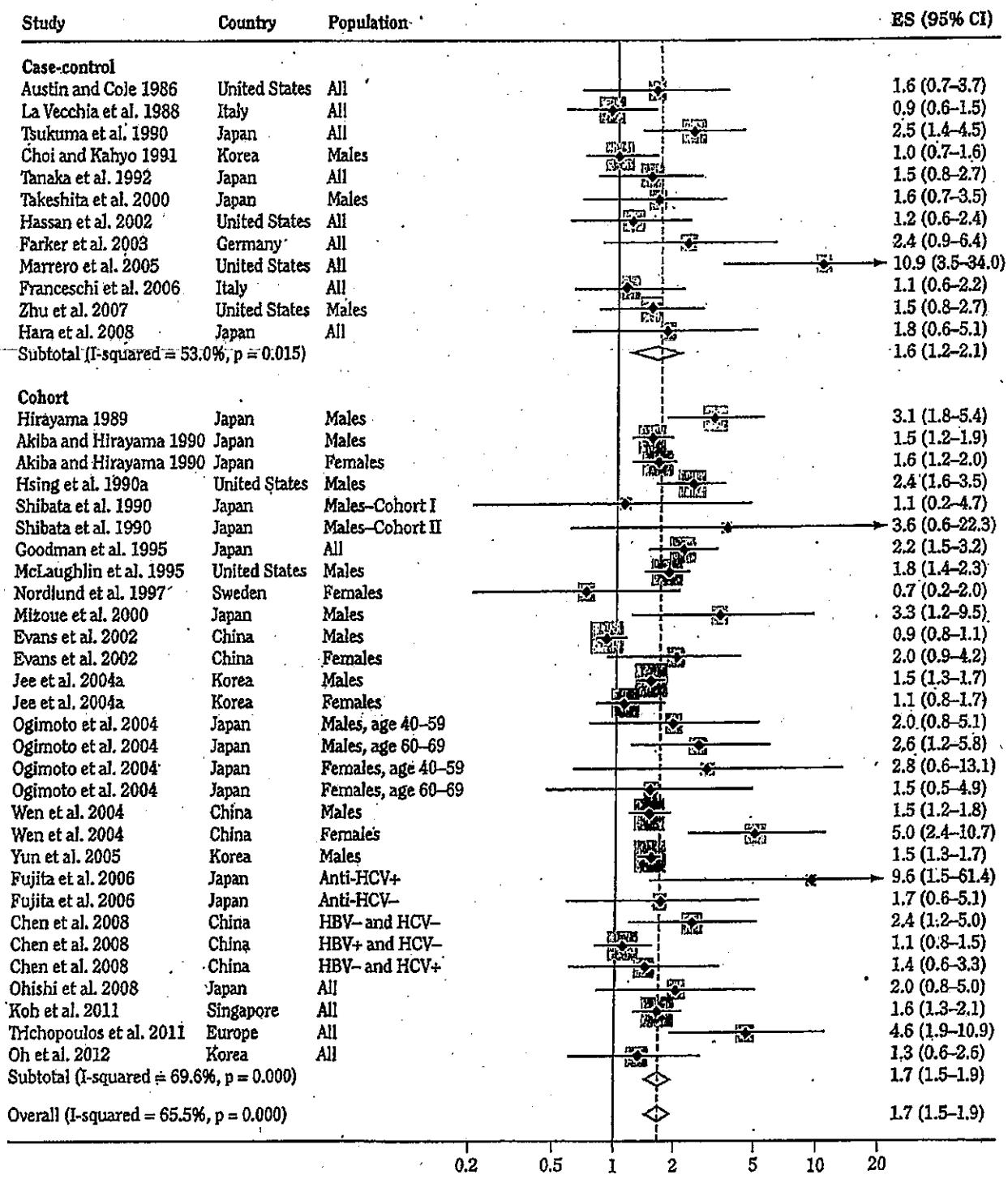
Because of concern for residual confounding of smoking effects by coinfection with viral hepatitis, the association between smoking and HCC was evaluated in the present review among persons who did not have evidence for chronic viral hepatitis. In an analysis combining data from 13 studies (9 case-control 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).

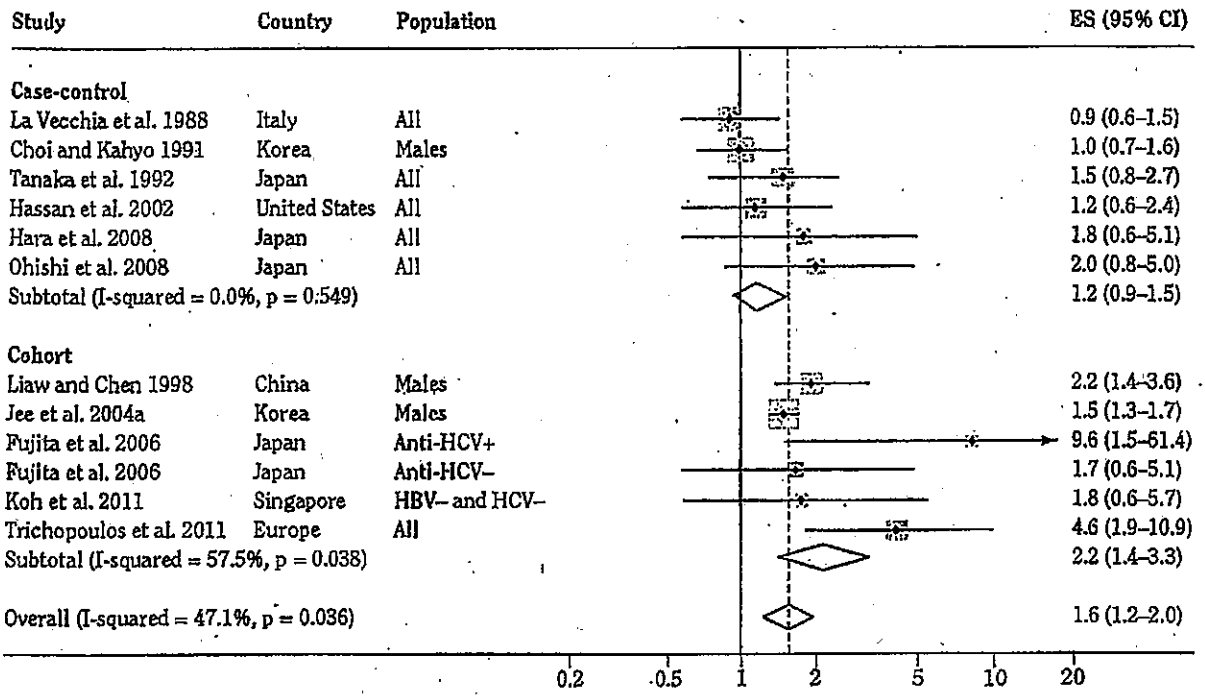
In countries in sub-Saharan Africa, the present data analysis was limited to case-control studies that evaluated ever smoking. The number of cases of HCC in these studies ranged from 46–240, and all of them adjusted for HBV or HCV infection and consumption of alcohol. Each study suggested an association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

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



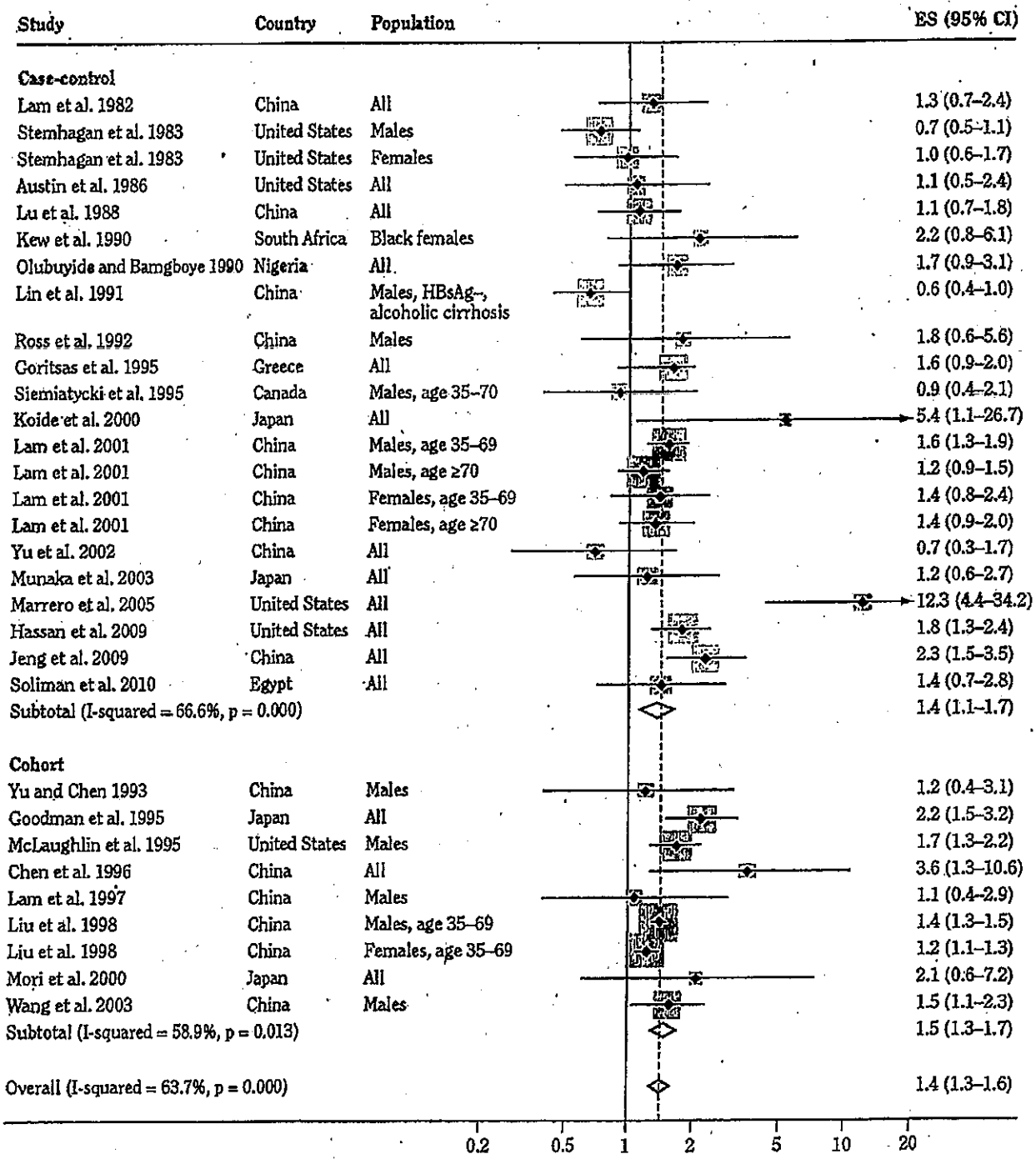
Note: Weights are from random effects analysis. CI = confidence interval; ES = effect size; HBV = 675 hepatitis B virus; HCV = hepatitis C virus.

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)



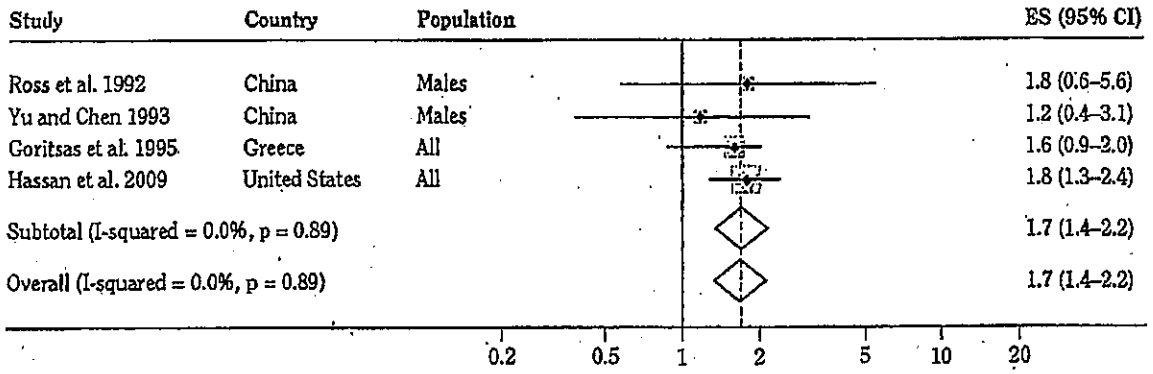
Note: Weights are from random effects analysis. CI = confidence interval; ES = effect size; HBV = 683 hepatitis B virus; HCV = hepatitis C virus 684.

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 = 690 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.

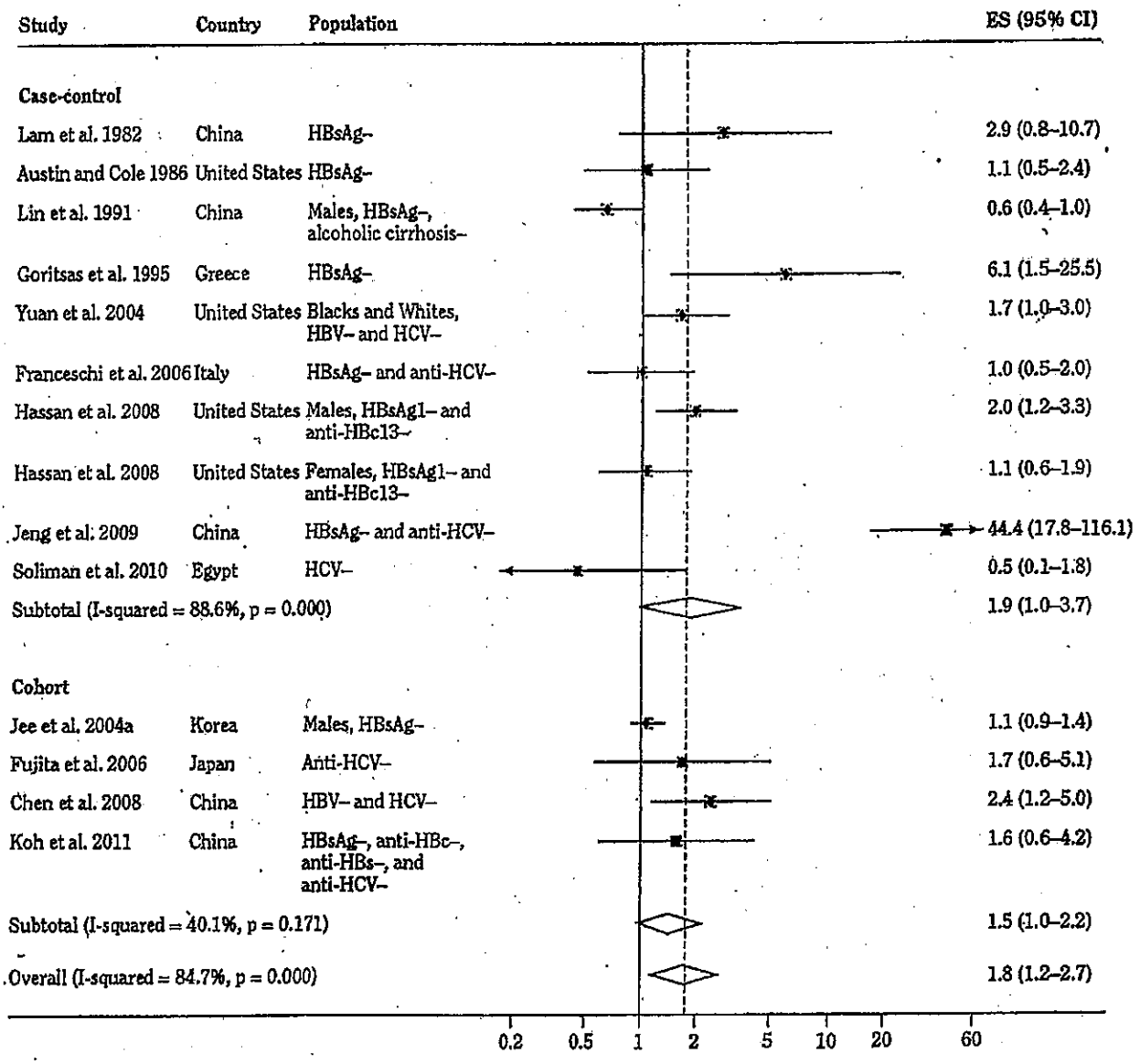
none of them were statistically significant—likely because of the limited number of cases. Overall, the RR from the three studies with data available (Kew et al. 1990; Olubuyide and Bamgboye 1990; Soliman et al. 2010) for countries in Africa was 1.7 (95% CI, 1.1–2.5).

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).

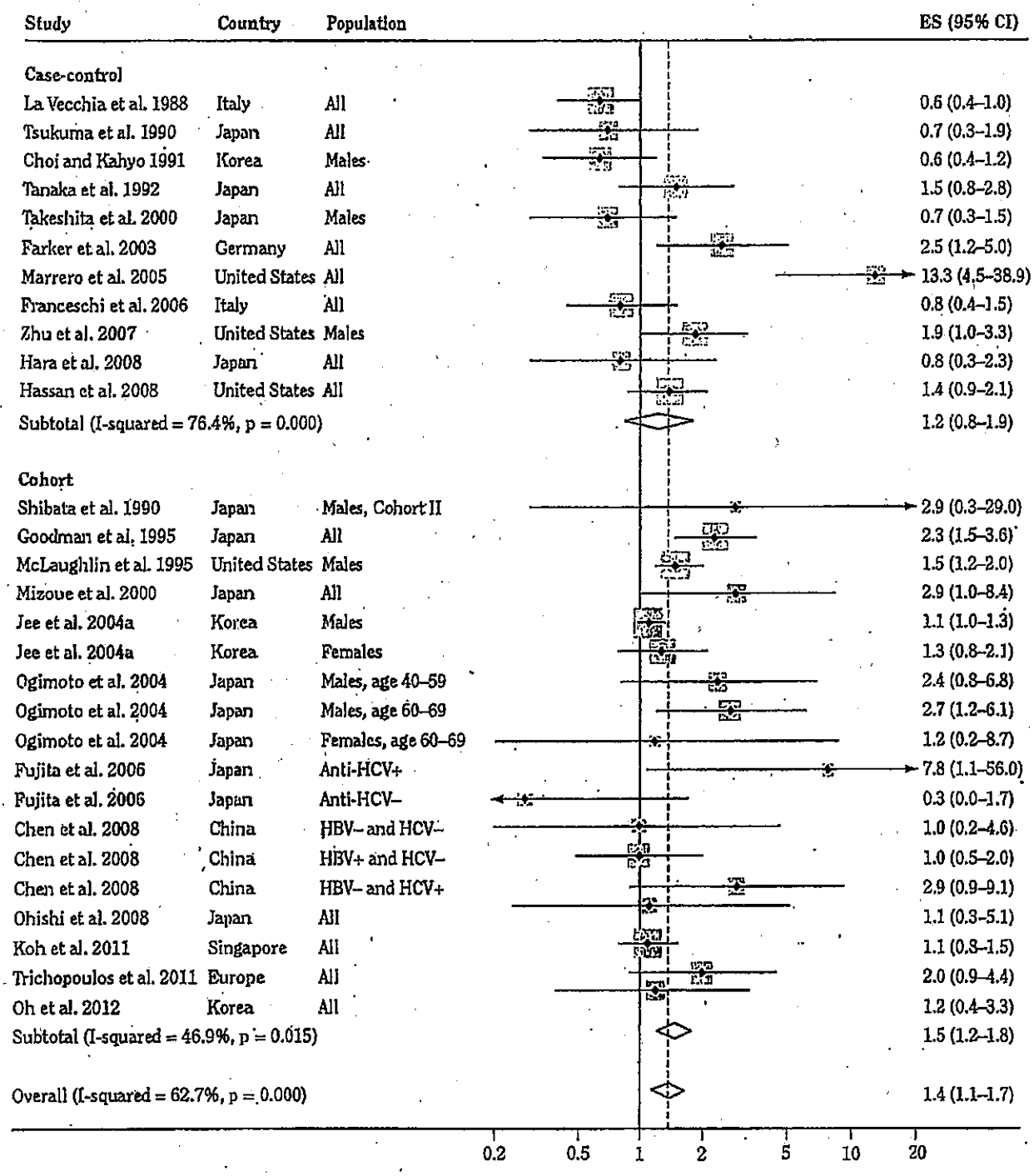
Similar to the experience in Greece, several studies from other regions suggested a higher risk of liver cancer with smoking among HBV-negative persons than among those who were HBV positive (Lam et al. 1982; Yu et al. 1991a; Chen et al. 2008). Some other studies, however, failed to find any difference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