Chapter 2
Health effects of exposure to secondhand smoke (SHS)

Introduction

In this chapter the Working Group summarises the major reviews that have been conducted in the last 10 years on the health effects of secondhand smoke (SHS). Where substantial new studies have been reported in the last few years, we describe these also, but do not attempt a formal assessment of the evidence overall. First, the literature on the relation between SHS and cardiovascular diseases is reviewed, since these conditions, and acute myocardial infarction (AMI) in particular, are leading contributors to the burden of disease caused by SHS. The chapter then provides an overview of effects of SHS on respiratory conditions and child health. Lastly, the link between SHS and cancer is examined, including the accumulation of evidence over time, and what is known about the relationship with cancers at particular sites. The emphasis in this chapter lies on the already answered question of whether SHS is a cause of disease, and if so, what is the relation between level of exposure and risk of disease. However, briefly we consider the related question of how much ill health may be attributed to exposures to SHS. This quantity, the burden of disease due to SHS, may be an important consideration for policy-makers and depends heavily on local circumstances, particularly the prevalence of exposure.

Non-malignant effects of SHS exposure

Overview

Exposure to SHS adversely affects the health of children and adults (Table 2.1). The inhalation of this mixture of irritant, toxic particles, and gases has respiratory effects, as well as effects on other organ systems, including causing coronary heart disease (CHD) in adults and sudden infant death syndrome (SIDS) in infants. There has been extensive research on mechanisms by which SHS causes these adverse effects; that evidence has been most recently reviewed in the 2006 report of the US Surgeon General and is not covered specifically in this chapter. However, we note the evidence was sufficient to support a major conclusion of this report, that "[c]hildren exposed to secondhand smoke are at increased risk for sudden infant death syndrome (SIDS), acute respiratory infections, ear problems and more severe asthma. Smoking by parents causes respiratory symptoms and slows lung growth in their children" (U.S. Department of Health and Human Services, 2006).

This chapter briefly reviews the findings of the various reports on the consequences of exposure to SHS (Table 2.1). The many adverse effects of SHS, beyond the causation of cancer, strengthen the rationale for achieving smoke-free environments, including not only public and workplaces, but homes, so as to ensure that children are protected from exposure to SHS. The most recent reports, particularly the 2005 California Environmental Protection Agency (EPA) report and the 2006 report of the US Surgeon General, provide comprehensive coverage of the epidemiological evidence and relevant research findings related to the plausibility of causal associations of SHS with respiratory and cardiovascular effects.

Beyond these adverse health effects, tobacco smoke, which contains numerous irritants, has long been linked to odor and annoyance (U.S. Department of Health and Human Services, 1986). Both questionnaire surveys and laboratory studies, involving exposure to SHS, have shown annoyance and irritation of the eyes and upper and lower airways from involuntary smoking. In several surveys of nonsmokers, complaints about tobacco smoke at work and in public places were common (U.S. Department of Health

Table 2.1 Adverse effects from exposure to tobacco smoke published in major reports

Health effect	SGR 1984	SGR 1986	EPA 1992	Cal EPA 1997	UK 1998/ 2004	WHO 1999	IARC 2004	Cal EPA* 2005**	SGR 2006
Increased prevalence of Chronic respiratory symptoms	Yes/a	Yes/a	Yes/c	Yes/c	Yes/c	Yes/c		Yes/c	Yes/c
Decrement in pulmonary function	Yes/a	Yes/a	Yes/a	Yes/a	Yes/a*	Yes/c		Yes/a	Yes/c
Increased occurrence of acute respiratory illnesses	Yes/a	Yes/a	Yes/a	Yes/c		Yes/c		Yes/c	Yes/c
Increased occurrence of middle ear disease		Yes/a	Yes/c	Yes/c	Yes/c	Yes/c		Yes/c	Yes/c
Increased severity of asthma episodes and symptoms			Yes/c	Yes/c		Yes/c		Yes/c	Yes/c
Risk factor for new asthma			Yes/a	Yes/c				Yes/c	Yes/c
Risk factor for SIDS				Yes/c	Yes/a	Yes/c		Yes/c	Yes/c
Risk factor for lung cancer in adults		Yes/c	Yes/c	Yes/c	Yes/c		Yes/c	Yes/c	Yes/c
Risk factor for breast cancer for younger, primarily premenopausal women								Yes/c	
Risk factor for nasal sinus cancer								Yes/c	
Risk factor for coronary heart disease in adults				Yes/c	Yes/c			Yes/c	Yes/c

SGR: US Surgeon General's report; EPA: US Environmental Protection Agency; Cal EPA: California Environmental Protection Agency; WHO: World Health Organization; IARC: International Agency for Research on Cancer; UK: United Kingdom Scientific Committee on Tobacco and Health
*Added in 2004
**Only effects causally associated with SHS exposure are included
Yes/a = association
Yes/c = cause
Table adapted from U.S. Department of Health and Human Services (2006) and from ASHRAE (Environmental Tobacco Smoke, position document, page 9, Table 1), (2005).

and Human Services, 1986). About 50% of respondents complained about tobacco smoke at work, and a majority were disturbed by tobacco smoke in restaurants. The experimental studies show that the rate of eye blinking is increased by SHS, as are complaints of nose and throat irritation (U.S. Department of Health and Human Services, 1986). One study suggests that there may be increasing sensitivity to SHS as the general level of exposure declines (Junker *et al.*, 2001). The odor and irritation associated with SHS merit special consideration, because a high proportion of nonsmokers are annoyed by exposure to SHS, and control of concentrations in indoor air poses difficult problems in the management of heating, ventilating, and air-conditioning systems.

Childhood effects

Extensive epidemiological evidence has associated SHS exposure with respiratory and non-respiratory diseases and other adverse effects in children. Since the first reports in the 1960s, studies from around the world have shown that smoking by parents during pregnancy and after the child's birth causes disease, resulting in premature mortality and

substantial morbidity. Extensive data on exposure, including measurements of SHS components in the air and of biomarkers, document the key role of smoking by parents in exposing their children to SHS. Studies have also addressed the mechanisms by which SHS causes its adverse effects. This evidence is not reviewed in this chapter, as it has been recently reviewed in the reports of the California EPA and US Surgeon General.

Table 2.1 lists the diseases and other adverse effects causally associated with exposure to SHS. The list includes SIDS, an important cause of death in children under a year of age (Anderson & Cook, 1997); acute lower respiratory illnesses, a major cause of morbidity and mortality in children under five years of age; and acute and chronic middle ear disease, also a leading child health problem (U.S. Department of Health and Human Services, 2006). SHS exposure worsens asthma and may contribute to its causation. It also slows the rate of lung growth during childhood and adolescence and is associated with increased prevalence of respiratory symptoms.

The epidemiological evidence on outcomes that have been causally linked to SHS exposure is substantial, and provides quantitative estimates of the risk associated with SHS. In general, risk increases with the number of adult smokers in the household, and attributable risk estimates indicate that SHS exposure is a substantial contributor to the burden of respiratory morbidity in childhood, as well as a major cause of SIDS (California Environmental Protection Agency: Air Resources Board, 2005; U.S. Department of Health and Human Services, 2006).

Adulthood effects

Cardiovascular disease

The evidence indicating that SHS causes CHD in adults has been repeatedly reviewed since 1986. At that time, the US Surgeon General's report examined one case-control study and three cohort studies on the association of involuntary smoking and cardiovascular effects, concluding further research was needed to decide causality. A causal link between CHD and SHS was first reported in the California EPA report from 1997 (Table 2.1)

Causal associations between active smoking and fatal and nonfatal CHD outcomes have long been demonstrated (U.S. Department of Health and Human Services, 2004). Active cigarette smoking is considered to increase the risk of cardiovascular disease by promoting atherosclerosis; affecting endothelial cell functioning; increasing the tendency to thrombosis; causing spasm of the coronary arteries, which increases the likelihood of cardiac arrhythmias; and decreasing the oxygen-carrying capacity of the blood (U.S. Department of Health and Human Services, 1990). These same mechanisms have been considered to be relevant to SHS exposure and risk for CHD (Barnoya & Glantz, 2005; U.S. Department of Health and Human Services, 2006). Experimental studies support the relevance of these mechanisms (U.S. Department of Health and Human Services, 2006).

In 2005, the pathophysiological mechanisms by which SHS exposure might increase the risk of heart disease were summarised (Barnoya & Glantz, 2005). They suggested that passive smoking may promote atherogenesis; increase the tendency of platelets to aggregate, and thereby promote thrombosis; impair endothelial cell function; increase arterial stiffness leading to atherosclerosis; reduce the oxygen-carrying capacity of the blood; and alter myocardial metabolism, much as for active smoking and CHD. Several separate experiments, involving exposure of nonsmokers to SHS, have shown that passive smoking affects measures of platelet function in the direction of increased tendency toward thrombosis (Glantz & Parmley, 1995; Barnoya & Glantz, 2005). In a 2004 study, sidestream smoke was found to be 50% more potent than mainstream smoke in activating platelets (Rubenstein *et al.*, 2004). It was also proposed that carcinogenic agents, such as polycyclic aromatic hydrocarbons found in tobacco smoke, promote atherogenesis by effects on cell proliferation (Glantz & Parmley, 1995). These mechanistic considerations support both acute and chronic effects of SHS exposure on risk for cardiovascular disease.

Exposure to SHS may also worsen the outcome of an ischemic event in the heart: animal data have demonstrated that SHS exposure increases cardiac damage following an experimental myocardial infarction. Experiments on two species of animals (rabbits and cockerels) have demonstrated that not only does exposure to SHS at doses similar to exposure to humans accelerate the

growth of atherosclerotic plaques through the increase of lipid deposits, but it also induces atherosclerosis.

There is also impressive and accumulating evidence that SHS acutely affects vascular endothelial cell functioning (Celermajer *et al.*, 1996; Sumida *et al.*, 1998; Otsuka *et al.*, 2001). Thirty minutes of exposure to SHS in healthy young volunteers was found to compromise coronary artery endothelial function in a manner that was indistinguishable from that of habitual smokers, suggesting that endothelial dysfunction may be an important mechanism by which exposure to SHS increases CHD risk (Otsuka *et al.*, 2001).

In addition to its effects on platelets, SHS exposure affects the oxygen-carrying capacity of the blood through its carbon monoxide component. Even small increments, on the order of 1%, in the carboxyhemoglobin, may explain the finding that SHS exposure decreases the duration of exercise of patients with angina pectoris (Allred *et al.*, 1989). This is supported with evidence that cigarette smoking has been shown to increase levels of carbon monoxide in the spaces where ventilation is low or smoking is particularly intense (U.S. Department of Health and Human Services, 1986).

A 1985 report, based on a cohort study in southern California, was the first epidemiologic investigation to raise concerns that exposure to SHS may increase risk for CHD (Garland *et al.*, 1985). There are now more than 20 studies on the association between SHS and cardiovascular disease, including cohort and case-control studies. They cover a wide range of populations, both geographically and racially. One group of studies addressed the promotion of atherosclerosis and SHS exposure, using increased carotid intimal-medial thickness (IMT) as an indicator. These studies have shown both cross-sectional and longitudinal associations of IMT with SHS exposure (Howard *et al.*, 1994, 1998; Diez-Roux *et al.*, 1995).

As the evidence since the first report has mounted, it has been reviewed systematically by the American Heart Association (Taylor *et al.*, 1992), the Australian National Health and Medical Research Council (1997), the California EPA (California Environmental Protection Agency, 1997; California Environmental Protection Agency: Air Resources Board, 2005), the Scientific Committee on Tobacco and Health in the United Kingdom (Scientific Committee on Tobacco and Health, 1998) and most recently by the US Surgeon General (U.S. Department of Health and Human Services, 2006). Review of the evidence has uniformly led to the conclusion that there is a causal association between exposure to SHS and risk of cardiovascular disease (California Environmental Protection Agency , 1997; Scientific Committee on Tobacco and Health, 1998). The meta-analysis prepared for the 2006 US Surgeon General's report, estimated the pooled excess risk for coronary heart disease from SHS exposure from marriage to a smoker as 27% (95% CI=19-36%) (U.S. Department of Health and Human Services, 2006).

There is increasing epidemiologic evidence suggestive of a causal association between SHS exposure and stroke. At least eight epidemiologic studies (four case-control, two cohort, and two cross-sectional) have been published exploring this association (Lee *et al.*, 1986; Donnan *et al.*, 1989; Sandler *et al.*, 1989; Howard *et al.*, 1998; Bonita *et al.*, 1999; You *et al.*, 1999; Zhang *et al.*, 2005). A large cross-sectional study of 60 377 women in China, found an association between prevalent stroke in women and smoking by their husbands (Zhang *et al.*, 2005). The prevalence of stroke increased with greater duration of smoking and with an increasing number of cigarettes smoked daily. A cohort study was conducted of 19 035 lifetime nonsmokers using census data from Washington County, MD (Sandler *et al.*, 1989). Based on 297 cases among women exposed to SHS, a 24% increased risk of stroke was found compared with those unexposed (95% CI=3-49%). Null results were found for an association in men, but were limited to only 33 cases. A case-control study in New Zealand, which looked at 265 cases and 1336 controls, did find a two-fold increased risk of stroke in men exposed to SHS (Bonita *et al.*, 1999). Additionally, a 2004 prospective cohort study used serum cotinine levels for exposure classification (Whincup *et al.*, 2004). The 20 year study included 4729 men in the UK who provided baseline blood samples in 1978 to 1980. A consistent association was not found between serum cotinine concentration and stroke.

Respiratory disease

Exposure to SHS has been explored as a contributing factor

to respiratory morbidity in general, including respiratory symptoms and reduction of lung function, and also as a factor causing and exacerbating both chronic obstructive pulmonary disease (COPD) and asthma. The effects are plausible consequences of exposure to SHS, given the evidence on active smoking and respiratory health, and knowledge of the components and toxicity of SHS. To date, a range of adverse effects has been investigated. The evidence is most consistent in showing that SHS exposure of adults may contribute to respiratory symptoms, exacerbate underlying lung disease, and slightly reduce lung function (Table 2.1).

Secondhand smoke (SHS) and cancer

Historical perspective

The health effects of active smoking and the carcinogenicity of tobacco smoke became a focus of research in the first decades of the 20th century, as the first indications of the emerging lung cancer epidemic were identified. By the 1950s, substantial epidemiological and experimental research was in progress, leading to the conclusion in the 1960s that active smoking was a cause of lung cancer (Royal College of Physicians of London, 1962; U.S. Department of Health Education and Welfare, 1964). IARC published its first monograph on tobacco smoking in 1986 (IARC, 1986).

The potential for tobacco smoke inhaled by nonsmokers to cause disease was first considered in the US Surgeon General's report in 1972 (U.S. Department of Health Education and Welfare, 1972). That report reviewed the evidence on components of tobacco smoke in enclosed spaces and commented on the potential for inhaled pollutants from cigarette smoke to cause disease. Beginning in the late 1960s, epidemiological research addressed adverse effects of smoking in the home on the health of children. In 1981, published reports from Japan (Hirayama, 1981) and Greece (Trichopoulos *et al.*, 1981) indicated increased lung cancer risk in nonsmoking women married to cigarette smokers. These reports sparked a wave of additional epidemiological studies on lung cancer, as well as studies on exposure to SHS, using biomarkers and measurement of tobacco smoke components in indoor air.

By 1986, the evidence had mounted, and three reports published in that year concluded that SHS was a cause of lung cancer. In its Monograph 38, IARC concluded that "passive smoking gives rise to some risk of cancer" (IARC, 1986). The IARC Working Group supported this conclusion on the basis of the characteristics of sidestream and mainstream smoke, the absorption of tobacco smoke materials during involuntary smoking, and the nature of dose-response relationships for carcinogenesis. In the same year, a US National Research Council (NRC) committee (National Research Council, 1986) and the US Surgeon General (U.S. Department of Health and Human Services, 1986) also concluded that involuntary smoking increases the incidence of lung cancer in nonsmokers. In reaching this conclusion, the NRC cited the biological plausibility of the association between exposure to SHS and lung cancer and the supporting epidemiological evidence (National Research Council, 1986). Based on a meta-analysis of the epidemiological data adjusted for bias, the report concluded that the best estimate for the excess risk of lung cancer in nonsmokers married to smokers was 25%. The 1986 report of the US Surgeon General also characterised involuntary smoking as a cause of lung cancer in nonsmokers (U.S. Department of Health and Human Services, 1986). This conclusion was based on the extensive information already available on the carcinogenicity of active smoking, on the qualitative similarities between SHS and mainstream smoke, and on the epidemiological data on involuntary smoking.

Subsequently, the many further epidemiological studies on SHS and lung cancer have better characterised the quantitative risk associated with SHS, and refined understanding of the doses of carcinogens received by nonsmokers who inhale it. Many additional agencies have now concluded that SHS causes lung cancer and other diseases; adverse health effects have also been causally associated with SHS (Table 2.1). The last IARC review on the topic of SHS and cancer was in its Monograph 83, *Tobacco Smoke and Involuntary Smoking*, based on a Working Group that convened in 2002 (IARC, 2004). The list of cancers investigated for association with SHS is now lengthy, with reports covering many of the cancers caused by active smoking, breast cancer, and childhood cancers. The considerations around biological plausibility of a causal association of

SHS exposure with these cancers, reflect either local deposition of tobacco smoke components and metabolites (sinonasal cancer and gastrointestinal cancers) or their systemic distribution (cancers of the breast, bladder, pancreas, brain, liver, and ovary, and leukemias and lymphomas).

These conclusions on SHS and disease risk have had substantial impact, providing a strong rationale for making public and workplaces smoke-free. The significance of this research, and the related conclusions, have motivated widespread efforts by the multinational tobacco companies to discredit the scientific evidence on SHS and disease, particularly the findings of epidemiological studies (Brandt, 2007). These efforts have now been documented through reviews of the industry's internal documents, and these tactics were one element of the successful litigation in the USA against the industry, which was found guilty of fraud and racketeering (Kessler, 2006).

Prior reviews and methods for this review

The evidence on SHS and cancer has been serially reviewed. Reports have been prepared by various agencies including most recently IARC in 2002 (IARC, 2004), the California Environmental Protection Agency in 2005 (California Environmental Protection Agency: Air Resources Board, 2005), and the US Surgeon General in 2006 (U.S. Department of Health and Human Services, 2006). Additionally, reports in peer-reviewed literature have addressed the topic (Johnson, 2005; Taylor *et al.*, 2007). In preparing the evidence tables for this chapter, these reports provided a starting point for identifying those studies that should be considered. Additionally, literature searches were updated using search strategies described below. Quantitative summaries of the evidence were prepared when the data were sufficiently abundant and with adequate homogeneity of methodology and reporting of findings. The method of DerSimonian and Laird was employed for this pooling, using the statistical package Stata (DerSimonian & Laird, 1986).

Three major reports were the starting point for the literature review on cancer: 1) *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General* (U.S. Department of Health and Human Services, 2006), 2) *Proposed Identification of ETS as a Toxic Air Contaminant* (California Environmental Protection Agency: Air Resources Board, 2005), and 3) *IARC Monograph 83: Tobacco Smoke and Involuntary Smoking* (IARC, 2004). The literature on SHS and cancer contained in these reports was systematically updated. A computerised literature search of the electronic PubMed database was conducted through December 31, 2007, without time or language restrictions. A keyword search was performed on tobacco smoke pollution, secondhand smoking, passive smoking, household smoking, involuntary smoking, and environmental tobacco smoke, in combination with cancer-related keywords. These keywords included cancer, adenocarcinoma, lymphoma, leukemia, childhood, glioma, meningioma, brain, head, neck, oral, nasal sinus, nasopharyngeal, esophageal, lung, breast, kidney, stomach, gastrointestinal, liver, pancreas, colon, colorectal, rectal, bladder, ovarian, prostate, and cervical cancer. Identified studies were screened and bibliographies were examined for related articles. Finally, publications of authors focusing on the field of smoking and cancer were searched. The identified articles were abstracted in a uniform fashion. Data from never smokers were presented in preference to data from current or former smokers. When available, adjusted relative risks were abstracted rather than crude results.

Adult cancers

Lung cancer

Overview

In numerous prior reports, including IARC Monograph 83, the conclusion has been reached that SHS causes lung cancer in people who have never actively smoked (Table 2.1). The evidence has been found sufficient to infer causality based on the extensive evidence showing that active smoking causes lung cancer, the biological plausibility of a causal association of SHS with cancer risk, and the consistency of the epidemiological findings. Alternative explanations to causation, particularly confounding and information bias, have been repeatedly scrutinised and rejected.

A causal association of involuntary smoking with lung cancer derives biological plausibility from the presence of carcinogens in SHS and the lack of a documented threshold

dose for respiratory carcinogens in active smokers (U.S. Department of Health and Human Services, 1982, 1986, 2004; IARC, 1986). Moreover, genotoxic activity has been demonstrated for many components of SHS (Claxton *et al.*, 1989; Lofroth, 1989; Weiss, 1989; Bennett *et al.*, 1999; DeMarini, 2004). Experimental and real-world exposures of nonsmokers to SHS leads to their excreting 4-(N-methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a tobacco-specific carcinogen, in their urine (Carmella *et al.*, 2003; Hecht, 2003). Nonsmokers exposed to SHS also have increased concentrations of adducts of tobacco-related carcinogens (Maclure *et al.*, 1989; Crawford *et al.*, 1994). Additionally, using an animal model, researchers found that whole-body exposure in rats to cigarette smoke increases the risk of neoplastic proliferative lung lesions and induces lung cancer (Mauderly *et al.*, 2004).

Time trends of lung cancer mortality in nonsmokers have been examined, with the rationale that temporally increasing exposure to SHS should be paralleled by increasing mortality rates (Enstrom, 1979; Garfinkel, 1981). These data provide only indirect evidence on the lung cancer risk associated with involuntary exposure to tobacco smoke. Epidemiologists have directly tested the association between lung cancer and involuntary smoking utilising conventional designs: case-control and cohort studies. These studies not only provide evidence relevant to causation, but also provide the characterisation of the risk that is needed to quantify the burden of lung cancer associated with SHS.

The epidemiological studies have primarily used self- or surrogate-report of exposure as the key indicator. Marriage to a smoker, particularly for women, has been the most frequently used exposure indicator. Methodological investigations suggest that accurate information can be obtained by interview in an epidemiological study on the smoking habits of a spouse (i.e. never or ever smoker) (Pron *et al.*, 1988; Coultas *et al.*, 1989; Cummings *et al.*, 1989; Lubin, 1999). However, information concerning quantitative aspects of the spouse's smoking is reported with less accuracy. Misclassification of current or former smokers as never smokers may introduce a positive bias, because of the concordance of spouse smoking habits (Lee, 1998). The extent to which this bias explains the numerous reports of association between spousal smoking and lung cancer has been addressed; findings indicate that bias does not account for the observed association (Wald *et al.*, 1986; Lee, 1988; U.S. Environmental Protection Agency, 1992; Wu, 1999; U.S. Department of Health and Human Services, 2006).

In some countries, including the USA, smoking prevalence now varies markedly with indicators of income and education, more recently tending to rise sharply with decreasing level of education and income (U.S. Department of Health and Human Services, 1989, 2004). In general, exposure to SHS follows a similar trend, and critics of the findings on SHS and lung cancer have argued that uncontrolled confounding by lifestyle, occupation, or other factors may explain the association. In fact, data for the USA do indicate a generally less healthy lifestyle in those with greater SHS exposure (Matanoski *et al.*, 1995). However, other than a few occupational exposures at high levels, as well as indoor radon, risk factors for lung cancer in never smokers that might confound the SHS association cannot be proffered, and the relevance to past studies of these current associations of potential confounders with SHS exposure is uncertain.

Epidemiological evidence

The first major studies on SHS and lung cancer were reported in 1981. Hirayama's early report (Hirayama, 1981) was based on a prospective cohort study of 91 540 nonsmoking women in Japan. Standardised mortality ratios (SMRs) for lung cancer increased significantly with the amount smoked by the husbands. The findings could not be explained by confounding factors and were unchanged when follow-up of the study group was extended (Hirayama, 1984). Based on the same cohort, significantly increased risk was reported for nonsmoking men married to wives smoking 1-19 cigarettes and ≥20 cigarettes daily (Hirayama, 1984). In 1981, increased lung cancer risk in nonsmoking women married to cigarette smokers was reported (Trichopoulos *et al.*, 1981). These investigators conducted a case-control study in Athens, Greece, which included cases with a final diagnosis of lung cancer other than adenocarcinoma or terminal bronchial carcinoma, and controls from the Hospital for Orthopedic Disorders. The positive findings reported in 1981 were unchanged with subsequent

expansion of the study population (Trichopoulos *et al.*, 1983).

Subsequently, numerous case-control and cohort studies have addressed SHS and lung cancer. Among the additional studies, a US multicenter study merits specific discussion because of its size (651 cases and 1253 controls), and its methodology, which addressed the extant criticisms at the time of its being conducted (Fontham *et al.*, 1994). The study found a significant increase in overall relative risk for nonsmoking women married to smokers (odds ratio (OR)=1.26; 95% CI=1.04-1.54). Significant risk was also associated with occupational exposure to SHS.

Beginning with the 1986 NRC report, there have been periodic meta-analyses of the evidence on SHS and lung cancer. One of the first comprehensive meta-analyses was carried out by the US Environmental Protection Agency for its 1992 risk assessment (U.S. Environmental Protection Agency, 1992). A meta-analysis of the 31 studies published to that time was central in the Agency's decision to classify SHS as a Group A carcinogen - namely a known human carcinogen. The meta-analysis considered the data from the epidemiologic studies by tiers of study quality and location and used an adjustment method for misclassification of smokers as never smokers. Overall, the analysis found a significantly increased risk of lung cancer in never smoking women married to smoking men; for the studies conducted in the USA, the estimated relative risk was 1.19 (90% CI=1.04-1.35).

In 1997, a comprehensive meta-analysis was carried out which included 37 published studies (Hackshaw *et al.*, 1997). An excess risk of lung cancer was estimated for nonsmokers married to smokers as 24% (95% CI=13-36%). Adjustment for potential bias and confounding by diet did not alter the estimate. This meta-analysis was part of the basis for the conclusion by the UK Scientific Committee on Tobacco and Health that SHS is a cause of lung cancer (Scientific Committee on Tobacco and Health, 1998). A subsequent IARC meta-analysis (IARC, 2004) including 46 studies and 6257 cases, yielded similar results: 24% (95% CI=14-34%). Incorporating the results from a cohort study with null results overall, but only 177 cases (Enstrom & Kabat, 2003), did not change the findings (Hackshaw, 2003).

The most recent summaries from the 2006 Surgeon General's report are provided in Table 2.2. The summary estimates continue to show an excess risk of around 20% (e.g. pooled relative risk estimates around 1.2) for nonsmokers married to smokers. There is not strong evidence for heterogeneity by gender or location. Workplace exposure is also associated with increased risk. The evidence is less convincing for childhood exposure.

Several other recent meta-analyses further quantify the association between SHS and lung cancer. A meta-analysis of 22 studies published through 2003 on workplace SHS exposure and lung cancer was performed (Stayner *et al.*, 2007). The pooled relative risk (RR) was 1.24 (95% CI=1.18-1.29) associated with exposure to workplace SHS. Among highly exposed workers, the RR was 2.01 (95% CI=1.33-2.60). Another meta-analysis was carried out to calculate a pooled estimate of RR of lung cancer associated with exposure to SHS in never smoking women exposed to smoking spouses (Taylor *et al.*, 2007). Using 55 studies (seven cohort, 25 population-based case-control, and 23 non-population-based case-control studies) published through 2006, the authors found a pooled RR for lung cancer associated with SHS from spouses of 1.27 (95% CI=1.17-1.37). For North America the RR was 1.15 (95% CI=1.03-1.28), for Asia, 1.31 (95% CI=1.16-1.48) and for Europe, 1.31 (95% CI=1.24-1.52).

Since the two meta-analyses above and the 2006 Surgeon General's report on SHS, two new case-control studies have been published that confirm the association between SHS and lung cancer. A multicenter, population-based case-control study in Mexico City was conducted. For males and females combined, the OR for lung cancer associated with SHS exposure at home was 1.8 (95% CI=1.3-2.6) after adjusting for age, sex, educational level, and access to social security (Franco-Marina *et al.*, 2006). Among male and female never smokers, the crude OR for lung cancer associated with SHS exposure at home was 1.8 (95% CI=1.1-3.0) (Franco-Marina, 2008). A study in never smoking Chinese women aged 18-70 years, included cases diagnosed with lung cancer from hospitals in Beijing, Shanghai, and Chengdu, and population controls matched for age and sex (Fang *et al.*, 2006). The OR for lung cancer associated with >50 person-years of exposure to SHS from home or work was 1.77 (95% CI=1.07-2.92).

Table 2.2 Quantitative estimate of the risk of lung cancer with differing sources of exposure to secondhand smoke (adapted from U.S. Department of Health and Human Services, 2006)

Study	Data source	Exposure vs. Referent	RR	95% CI
Hackshaw *et al*., 1997	37 studies	Smoking vs. nonsmoking spouse	1.24	1.13-1.36
IARC, 2004	38 studies	Smoking vs. nonsmoking husband	1.23	1.13-1.34
US Surgeon General, 2006	Case-control (44 studies)	Smoking vs. nonsmoking spouse	1.21	1.13-1.30
Spouse	Cohort (8 studies)	Smoking vs. nonsmoking spouse	1.29	1.12-1.49
54 studies	Men	Smoking vs. nonsmoking wife	1.37	1.05-1.79
	Women	Smoking vs. nonsmoking husband	1.22	1.13-1.31
	USA and Canada	Smoking vs. nonsmoking spouse	1.15	1.04-1.26
	Europe	Smoking vs. nonsmoking spouse	1.16	1.03-1.30
	Asia	Smoking vs. nonsmoking spouse	1.43	1.24-1.66
US Surgeon General, 2006	Nonsmokers (25 studies)	Workplace SHS vs. not	1.22	1.13-1.33
Workplace	Nonsmoking Men (11 studies)	Workplace SHS vs. not	1.12	0.86-1.50
25 studies	Nonsmoking Women (25 studies)	Workplace SHS vs. not	1.22	1.10-1.35
	Nonsmokers USA & Canada (8 studies)	Workplace SHS vs. not	1.24	1.03-1.49
	Nonsmokers Europe (7 studies)	Workplace SHS vs. not	1.13	0.96-1.34
	Nonsmokers Asia (10 studies)	Workplace SHS vs. not	1.32	1.13-1.55
US Surgeon General, 2006	Men and Women	Maternal smoking	1.15	0.86-1.52
Childhood	Men and Women	Paternal smoking	1.10	0.89-1.36
24 studies	Men and Women	Either parent smoking	1.11	0.94-1.31
	Women	Maternal smoking	1.28	0.93-1.78
	Women	Paternal smoking	1.17	0.91-1.50
	USA (8 studies)	Either parent smoking	0.93	0.81-1.07
	Europe (6 studies)	Either parent smoking	0.81	0.71-0.92
	Asia (10 studies)	Either parent smoking	1.59	1.18-2.15

Three prospective cohort studies examining the relationship between SHS in nonsmokers have also been published since the meta-analyses by Taylor *et al.* (2007) and Stayner *et al.* (2007). Most recently, in Japan, a population-based cohort study of 28 414 lifelong nonsmoking women aged 40-69 years was conducted, collecting information on exposures from spousal smoking, workplace exposure, and childhood exposure (Kurahashi *et al.*, 2008). The hazard ratio (HR) for all lung cancer types associated with living with a smoking husband was 1.34 (95% CI=0.81-2.21). The HR for adenocarcinoma associated with living with a smoking husband was significantly elevated at 2.03 (95% CI=1.07-3.86). For all lung cancer types, the HR associated with SHS in the workplace was 1.32 (95% CI=0.85-2.04), while the HR specifically for adenocarcinoma associated with SHS in the workplace was 1.93 (95% CI=0.88-4.23).

A cohort study in 10 European countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) was conducted to examine the relationships of SHS and air pollution with lung cancer (Vineis *et al.*, 2007). It was found that among never smokers, the HR of lung cancer for SHS exposure at home or work was 1.05 (95% CI=0.60-1.82); at home: 0.84 (95% CI=0.38-1.9), at work: 1.28 (95% CI=0.67-2.4) (Vineis, 2008).

Also examined was the association between household exposure to SHS and lung cancer mortality in two cohorts of New Zealand lifelong nonsmokers aged 45-77 years, by linking census records, which included smoking information, to mortality records (Hill *et al.*, 2007). The age and ethnicity standardised RR for mortality from lung cancer associated with home exposure to SHS was 1.00 (95% CI=0.49-2.01) in the 1981-1984 cohort and 1.16 (95% CI=0.70-1.92) in the 1996-1999 cohort.

For this chapter, the prior meta-analyses were not updated with these new estimates, as the existing estimates are based on an already substantial body of research; they are robust to additional data and IARC has already concluded that passive smoking causes cancer.

The extent of the lung cancer burden associated with involuntary smoking remains subject to some uncertainty, but estimates have been made that are useful indications of the magnitude of the disease risk (U.S. Department of Health and Human Services, 1986; Weiss, 1986; California Environmental Protection Agency : Air Resources Board, 2005). In 1990, researchers reviewed the risk assessments of lung cancer and passive smoking and estimated the numbers of lung cancer cases in US nonsmokers attributable to passive smoking (Repace & Lowrey, 1990). The range of the nine estimates, covering both never smokers and former smokers, was from 58 to 8124 lung cancer deaths for the year 1988, with an overall mean of 4500 or 5000 excluding the lowest estimate of 58. The 1992 estimate of the California EPA, based on the epidemiologic data, was about 3000, including approximately 1500 and 500 deaths in never smoking women and men, respectively, and about 1000 in long-term former smokers of both sexes (U.S. Environmental Protection Agency, 1992). The California EPA estimated that at least 3423, and perhaps as many as 8866, lung cancer deaths were caused by SHS in the USA (California Environmental Protection Agency: Air Resources Board, 2005). These calculations illustrate that passive smoking must be considered an important cause of lung cancer death from a public health perspective; exposure is involuntary and not subject to control.

Bladder cancer

The US Surgeon General (U.S. Department of Health and Human Services, 2006), California EPA (California Environmental Protection Agency: Air Resources Board, 2005), and IARC (2004) reports did not address cancer of the bladder. The literature search for this chapter identified nine studies with information on the association between exposure to SHS and bladder cancer (Tables 2.3a,b) with cases identified between 1963 and 2004. A meta-analysis of these studies was conducted to obtain a pooled estimate of risk for bladder cancer associated with exposure to SHS. Since several studies presented risk estimates stratified by mutually exclusive exposure categories (Burch *et al.*, 1989; Zeegers *et al.*, 2002; Chen *et al.*, 2005; Samanic *et al.*, 2006), the Working Group pooled these estimates using random effects meta-analysis. Risk estimates were then pooled across studies using random effects meta-analysis (Figure 2.1). The most comprehensive exposure from each study was used in calculating the combined risk estimate of 0.97 (95% CI=0.74-1.28, *p for heterogeneity*=0.153). Neither

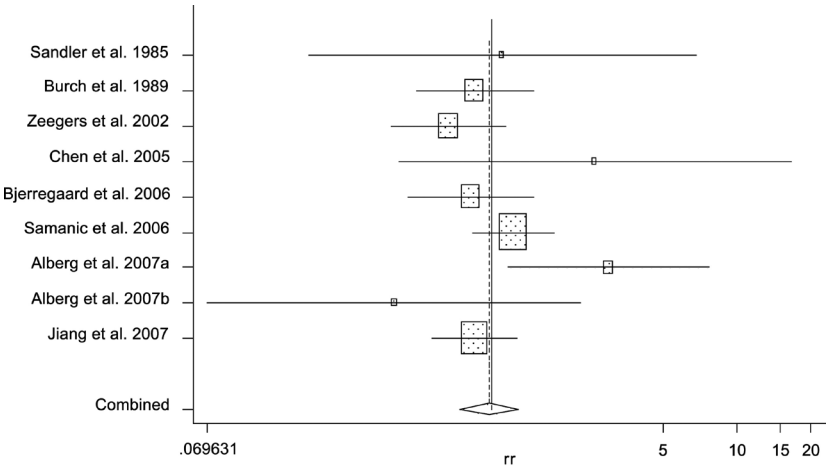


Figure 2.1 Pooled risk estimates from random effects meta-analysis of exposure to SHS and bladder cancer

Alberg et al., 2007a and 2007b refer to estimates from the 1963 and 1975 cohorts respectively. All data included in the reference Alberg et al., 2007
Sandler et al., 1985 refers to estimates cited in the reference Sandler et al., 1985a

the Begg's nor Egger's tests indicated publication bias with p-values of 0.602 and 0.654, respectively.

Brain cancer

The California EPA report on SHS in 2005 reviewed the previous literature regarding the association between SHS exposure and brain cancer in adults; four studies were considered. In the first published study, brain tumor mortality in a large scale cohort of nonsmoking married women in Japan was examined (Hirayama, 1984). It was reported that the rate ratio (RR) of death from brain cancer was increased among women with smoking husbands when compared to women who were married to nonsmokers. For a husband's consumption of 1-14 cigarettes/day the RR was 3.03 (90% CI=1.07-8.58), for 15-19 cigarettes/day the RR was 6.25 (90% CI=2.01-19.43), and the RR was 4.23 (90% CI=1.53-12.19) for 20+ cigarettes/day. However, there were only 34 cases of death from brain cancer. The 2005 California EPA report concluded that the epidemiological evidence for an association between SHS and risk of brain tumors was weak and inadequately researched, the same conclusion reached earlier in the 1997 California EPA report on SHS. Since the 2005 California EPA report, only one new report was identified. Associations between SHS exposure and the risk of intracranial meningioma in a population-based case-control study that included 95 cases and 202 controls matched on age and sex were examined (Phillips *et al.*, 2005). Among never smokers, exposure to SHS from smoking by a spouse was associated with a significantly increased risk of intracranial meningioma (OR=2.0; 95% CI=1.1-3.5). Risk increased with increasing years of exposure (*p for trend*=0.02). Neither exposure to SHS from another household member nor exposure at work was associated with risk, with ORs of 0.7 (95% CI=0.4-1.1) and 0.7 (95% CI=0.4-1.2), respectively (Tables 2.4a,b).

Breast cancer

In considering whether passive smoking causes breast cancer, the evidence for active smoking needs to be considered in assessing the plausibility of an association of breast cancer risk with SHS in nonsmokers. There is some evidence to suggest that an association between tobacco smoke and breast cancer is biologically plausible. Studies have shown that carcinogens in tobacco smoke reach breast tissue (Petrakis *et al.*, 1978, 1988 ; Li *et al.*, 1996) and are mammary mutagens (Nagao *et al.*, 1994; Dunnick *et al.*, 1995; el-Bayoumy *et al.*, 1995). However, other studies using biomarkers have found an association between smoking and decreased levels of estrogen (MacMahon *et al.*, 1982 ; Michnovicz *et al.*, 1986), which implies that active smoking might decrease the risk of breast cancer.

Table 2.3a Exposure to SHS and bladder cancer - Cohort studies

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Zeegers *et al*,. 2002 The Netherlands 1986-1992	3346 adults 55-69 years at enrollment (619 microscopically confirmed incident carcinomas of the urinary bladder, ureters, or urethra); 6.3 years of follow-up with no subjects lost	Self-administered questionnaire	Never-smoking partner (adulthood)	1	Age and gender	Results for never smokers
			Ex-smoking partner (adulthood)	0.95 (0.46-2.0)		
			Current-smoking partner (adulthood)	0.74 (0.29-1.9)		
			Parents did not smoke (childhood)	1		
			Parents smoked (childhood)	1.2 (0.56-2.4)		
			Low exposure to SHS at work (adulthood)	1		
			High exposure to SHS at work (adulthood)	1.4 (0.70-2.6)		
			No exposure to SHS at home or at work (adulthood)	1		
			1 to <3 hours per day of exposure to SHS at home or work (adulthood exposure)	0.69 (0.33-1.4)		
			3+ hours per day of exposure to SHS at home or work (adulthood exposure)	0.64 (0.29-1.4)		
Bjerregaard *et al*., 2006 Denmark, France, Sweden 1991-2004	126 908 adults 25-70 years at enrollment (115 cases of primary bladder cancer in never smokers); average follow-up time was 6.3 years	Self- and interviewer-administered questionnaire	No SHS exposure (at baseline) at home and/or work	1		Results for never smokers
			SHS exposure (at baseline) at home and/or work (adulthood exposure)	0.82 (0.46-1.48)		
			No SHS exposure during childhood	1	Fruit and vegetable intake, SHS exposure in childhood	
			SHS exposure during childhood (from parents or others)	2.02 (0.94-4.35)		

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Alberg *et al.*, 2007 Maryland, USA 1963-1978 cohort	24 823 never smoking women, aged ≥ 25 years at enrollment with no prior cancer (23 cases of invasive bladder cancer)	Self-administered questionnaire	Never smokers with noncurrent SHS exposure in the home	1	Age, education, marital status	Results for never smokers
			Current SHS exposure in the home (any source)	2.3 (1.0-5.4)		
			Former SHS exposure in the home (any source)	0.3 (0.1-2.5)		
			Current SHS exposure in the home (any source)	1.8 (0.8-4.5)		
			Exposed to SHS in the home from spouse only	1.1 (0.3-3.8)		
			Exposed to SHS in the home from other (than spouse) household members only	3.0 (1.2-7.9)		
Alberg *et al.*, 2007 Maryland, USA 1975-1994 cohort	26 381 women, aged ≥ 25 years at enrollment with no prior cancer (30 cases of invasive bladder cancer)	Self-administered questionnaire	Never smokers with noncurrent SHS exposure in the home	1	Age, education, marital status	Results for never smokers
			Current SHS exposure in the home (any source)	0.9 (0.4-2.3)		
			Former SHS exposure in the home (any source)	0.8 (0.3-2.0)		
			Current SHS exposure in the home (any source)	0.9 (0.3-2.2)		
			Exposed to SHS in the home from spouse only	1.2 (0.4-3.6)		
			Exposed to SHS in the home from other (than spouse) household members only	0.4 (0.1-3.3)		

Table 2.3b Exposure to SHS and bladder cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Sandler *et al.*, 1985a North Carolina, USA 1979-1981	6 patients 15-59 years with cancer of the urinary tract; 40% response rate	489 friend and community controls individually matched on gender, age, and race; 75% response rate	Self-administered questionnaire	Nonsmoking spouse or never married Spouse smoked regularly (at least 1 cig/day for at least 6 months) any time during marriage	1 1.1 (0.2-7.6)	Age and education	Only married individuals were eligible to be considered "exposed"
Sandler *et al*, 1985b North Carolina, USA 1979-1981	5 patients 15-59 years with cancer of the urinary tract; 70% response rate	438 friend and community controls individually matched on gender, age, and race; control response rate not stated	Self-administered questionnaire	Not exposed to SHS from father during first 10 yrs of life SHS exposure from father during first 10 yrs of life	1 0.8 (0.1-5.7)		None of the bladder cancer cases were exposed to SHS from the mother
Burch *et al.*, 1989 Alberta and Ontario, Canada 1979-1982	826 adults 35-79 years with primary bladder cancer without recurrent malignant neoplasms of the bladder or invasion of the bladder from primary prostatic cancer; 67% response rate	826 population controls individually matched for age, gender, and area of residence; 53% response rate	Interviewer-administered questionnaire	**Among nonsmokers:** No SHS exposure at home **Males:** exposure at home **Females:** exposure at home No SHS exposure at work **Males:** exposure at home **Females:** exposure at home	 1 0.94 (0.45-1.95) 0.75 (0.33-1.71) 1 0.97 (0.50-1.91) 0.93 (0.48-1.79)		
Chen *et al.*, 2005 Taiwan 1996-1999	14 adults ≥50 years with newly diagnosed bladder cancer	202 hospital controls (fracture and cataract patients) ≥50 years	Interviewer-administered questionnaire	**Men:** No SHS exposure SHS exposure **Women:** No SHS exposure SHS exposure	 1 7.16 (1.87-27.4) 1 1.09 (0.42-2.80)	Age, BMI, cumulative arsenic, hair dye usage, education	Interaction present for arsenic measured by secondary methylation index Results among nonsmokers presented

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Samanic *et al*., 2006 Spain 1998-2000	1219 White adults aged 21-80 years with incident bladder cancer without previous cancer of the lower urinary tract, or patients with bladder tumors secondary to other malignancies; 84% response rate	1271 hospital controls (with conditions considered unrelated to smoking), individually matched on age, gender, race, and hospital; 88% response rate	Interviewer-administered questionnaire	**Men:** No childhood SHS	1	Age, hospital region, fruit or vegetable consumption, and high-risk occupation *p for trend*= 0.92	Sum of the years spent at each childhood residence up to age 18
				<18 yrs SHS exposure	1.2 (0.6-2.3)		
				18 yrs SHS exposure	0.9 (0.3-2.6)		
				No residential adulthood SHS	1		Sum of the years spent at each adult residence times N of smokers per / res.
				>0 to 26 person-yrs of adulthood residential SHS	1.1 (0.5-2.4)		
				>26 to 54 person-yrs of adulthood residential SHS	0.8 (0.3-2.2)		
				>54 person-yrs of residential adulthood SHS	1.3 (0.5-3.2)		
				p for trend	0.74		
				No occupational adulthood SHS	1		Sum of the years spent at each job times N of smokers per job
				>0 to 135 person-yrs of occupational adulthood SHS	0.6 (0.2-1.6)		
				>135 to 240 person-yrs of occupational adulthood SHS	0.2 (0.1-0.7)		
				>240 person-yrs of occpationaladulthood SHS	0.6 (0.2-1.4)		
				p for trend	0.58		
				Women: No childhood SHS	1		
				<18 yrs childhood SHS	0.7 (0.3-1.4)		
				18 yrs childhood SHS	0.6 (0.2-1.7)		
				p for trend	0.24		
				No residential adulthood SHS	1		
				>0 to 26 person-yrs of residential adulthood SHS	2.2 (0.8-6.2)		

Table 2.3b Exposure to SHS and bladder cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Samanic *et al.*, 2006 Spain 1998-2000				>26 to 54 person-yrs of residential adulthood SHS	1.9 (0.7-4.8)		
				>54 person-yrs of residential adulthood SHS	0.8 (0.3-1.9)		
				p for trend	0.27		
				No occupational adulthood SHS	1		
				>0 to 135 occupational person-yrs of adulthood SHS	1.7 (0.7-4.0)		
				>135 to 240 person-yrs of occupational adulthood SHS	1.7 (0.6-4.4)		
				>240 person-yrs of occupational adulthood SHS	3.3 (1.1-9.5)		
				p for trend	0.03		
Jiang *et al.*, 2007 California, USA 1987-1999	148 never smoking Asian adults aged 25-64 years, with histologically-confirmed bladder cancer; 89.7% response rate	292 never smoking population controls, matched for age, gender, race, and area of residence; 96.4% response rate	Interviewer-administered questionnaire	**No SHS exposure during childhood**	1	Age, gender, race, education, adulthood SHS	Confidence intervals not provided
				SHS exposure during childhood	0.91		
				SHS exposure during childhood (1 smoker)	0.88		
				SHS exposure during childhood (>1 smoker)	0.97		
				No SHS exposure during adulthood in a domestic setting	1	Age, gender, education, childhood SHS, adulthood SHS (occupational and social settings)	
				SHS exposure during adulthood (domestic setting)	0.85		
				SHS exposure during adulthood (domestic setting, <10 yrs)	0.88		

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Jiang *et al.*, 2007 California, USA 1987-1999				SHS exposure during adulthood (domestic setting, ≥10 yrs)	0.82		
				No SHS exposure during adulthood in an occupational setting	1	Age, gender, education, childhood SHS, adulthood SHS (domestic and social settings)	
				SHS exposure during adulthood (occupational setting)	0.98		
				SHS exposure during adulthood (occupational setting, <10 yrs)	0.93		
				SHS exposure during adulthood (occupational setting, ≥10 yrs)	0.98		
				No SHS exposure during adulthood in a social setting	1	Age, gender, education, childhood SHS, adulthood SHS (domestic and occupational settings)	
				SHS exposure during adulthood (social setting)	1.06		
				SHS exposure during adulthood (social setting, <10 yrs)	1.29		
				SHS exposure during adulthood (social setting, ≥10 yrs)	0.92		
				Low (0) cumulative index of SHS exposure	1	Age, gender, education	
				Intermediate (1-3) cumulative index of SHS exposure	1.61		
				High (4-8) cumulative index of SHS exposure	1.28		

Table 2.4a Exposure to SHS and brain cancer - Cohort studies

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (90% CI)	Adjustment for potential confounders	Comments
Hirayama, 1984 Japan 1966-1981	91 540 nonsmoking, married women ≥40 years (34 deaths due to brain tumors)	Interviewer-administered questionnaire	Nonsmoking husband Husband smokes 1-14 cig/day Husband smokes 15-19 cig/day Husband smokes ≥20 cig/day	1 3.03 (1.07-8.58) 6.25 (2.01-19.43) 4.32 (1.53-12.19)	Husband's age	Same data used in Hirayama, 1985
Hirayama, 1985 Japan 1966-1981	91 540 nonsmoking, married women ≥40 years (34 deaths due to brain tumors)	Interviewer-administered questionnaire	Nonsmoking husband Husband is ex-smoker or smokes 1-19 cig/day Husband smokes ≥20 cig/day	1 3.28 (1.21-8.92) 4.92 (1.72-14.11)	Husband's age	Same data used in Hirayama, 1984

Table 2.4b Exposure to SHS and brain cancer in adults - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Sandler *et al.*, 1985a North Carolina, USA 1979-1981	38 patients 15-59 years with eye, brain, and other nervous system cancers; 66% response rate	489 friend and community controls; 75% response rate	Self-administered questionnaire	Non exposed to SHS Spouse smoked regularly (at least 1 cig/day for at least 6 months) any time during marriage	1 0.7 (0.3-1.5)	Age, sex, active smoking	Smoking wives included
Ryan *et al.*, 1992 Australia 1987-1990	170 adults 25-74 years with newly diagnosed cancer of the brain and meninges (110 glioma cases and 60 meningioma cases); 90.5% response rate	417 community controls, frequency matched on age, gender, and postal code; 63.3% response rate	Interviewer-administered questionnaire	**RR (95% CI) for glioma** Non exposed to SHS Ever exposed to SHS 1-12 yrs SHS exposure 13-27 yrs SHS exposure 28+ yrs SHS exposure Nonsmokers, ever exposed to SHS	 1 1.24 (0.76-2.00) 1.33 (0.69-2.56) 1.17 (0.60-2.27) 1.21 (0.62-2.37) 1.30 (0.62-2.7)	Age, sex, active smoking	Active smokers included

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ryan *et al.*, 1992					**RR (95% CI) for meningioma**		
Australia 1987-1990				Non exposed to SHS	1		
				Ever exposed to SHS	1.91 (1.01-3.63)		
				1-12 yrs SHS exposure	1.55 (0.66-3.65)		
				13-27 yrs SHS exposure	2.15 (0.91-6.38)		
				28+ yrs SHS exposure	2.12 (0.98-4.71)		
				Nonsmokers, ever exposed to SHS	2.45 (0.98-6.14)		
Hurley *et al.*, 1996	416 histologically confirmed gliomas	422 population controls matched by age and sex	Questionnaires and interviews	Spouse does not smoke	1		Results among nonsmokers
Australia 1987-1991				Living with smoker	0.97 (0.61-1.53)		
Phillips *et al.*, 2005	95 adult patients never smokers/haven't smoked in last 10 years with intracranial meningioma; 84% overall response rate	202 community controls, individually matched on age and sex; 55% response rate from random digit dialing and 67% response rate from Medicare eligibility lists		Spouse does not smoke	1	Conditional regression matched on age and sex and adjustment for education	
Washington, USA 1995-1998				Spouse smokes	2.0 (1.1-3.5)		
				Spouse smoked <13 yrs	1.4 (0.7-3.1)		
				Spouse smoked 13-28 yrs	2.3 (0.9-5.9)		
				Spouse smoked >28 yrs	2.7 (1.0-7.1)		
				p for trend	0.02		
				No SHS exposure at home from other household members	1		
				SHS exposure at home from other household members (not spouse)	0.7 (0.4-1.1)		
				No SHS exposure at work	1		
				SHS exposure at work	0.7 (0.4-1.2)		

The 2001 and 2004 reports of the US Surgeon General reviewed further evidence related to smoking and estrogen, finding that smoking was associated with a decreased risk of endometrial cancer and an earlier age at menopause (U.S. Department of Health and Human Services, 2001, 2004). These anti-estrogenic consequences of active smoking have been construed as implying that breast cancer risk would be reduced for active smokers in comparison with never smokers. The evidence is not consistent, however, and uncertainty remains about the effect of smoking on blood estrogen levels. These possibly opposing biological consequences of active smoking may explain why review of the epidemiologic data has found an overall null effect of active smoking on the risk of breast cancer.

Since the 1960s, there have been more than 50 studies investigating the association between active smoking and breast cancer. In 2002, a pooled analysis of data from 53 studies was conducted and found a relative risk of 0.99 (95% CI=0.92-1.05) for women who were current smokers compared with women who were lifetime nonsmokers (Hamajima *et al.*, 2002). One possible explanation for the null results is that the anti-estrogenic effects of smoking may offset the potentially carcinogenic effects on the risk of breast cancer. Subsequently, the 2004 reports of the US Surgeon General and IARC concluded that the weight of evidence strongly suggests that there is no causal association between active smoking and breast cancer (IARC, 2004). One year later, the California EPA concluded that active smoking is a cause of breast cancer, although it did not carry out a full, systematic review (California Environmental Protection Agency: Air Resources Board, 2005). Two cohort studies published in 2004 found a significant increase in risk of breast cancer (Al-Delaimy *et al.*, 2004; Reynolds *et al.*, 2004). However, the US Surgeon General concluded that sufficient evidence has not accumulated to suggest a causal association between active smoking and breast cancer (U.S. Department of Health and Human Services, 2006).

More than 20 epidemiologic studies have been published specifically addressing the association between SHS and breast cancer. Several major reports, including the IARC Monograph 83, the 2005 California EPA report, and the 2006 US Surgeon General's report, have reviewed the evidence for an association between SHS exposure and breast cancer (IARC, 2004 ; California Environmental Protection Agency: Air Resources Board, 2005 ; U.S. Department of Health and Human Services, 2006). The California EPA conducted a meta-analysis using six cohort studies and 12 case-control studies that were deemed to provide the "best evidence." They found an increased risk of 25% (95% CI=8-44%) overall, and concluded that there is sufficient evidence for a causal association among premenopausal women (California Environmental Protection Agency: Air Resources Board, 2005). Among post-menopausal women, there was no indication of an association. In 2004, IARC concluded that the evidence is inconsistent, and although some case-control studies found positive effects, cohort studies overall did not find a causal association (IARC, 2004). Additionally, the lack of a positive dose-response relationship and association with active smoking weigh against the possibility of an increased risk of breast cancer from SHS exposure. Subsequently, the US Surgeon General came to similar conclusions (U.S. Department of Health and Human Services, 2006). Using data from seven prospective cohort studies and 14 case-control studies, a meta-analysis was performed. Sensitivity analyses showed that cohort studies overall found null results and studies that adjusted for potential confounding showed weaker associations (U.S. Department of Health and Human Services, 2006). Furthermore, the possibility of publication bias was evaluated, and found that less precise studies tended to have more positive results. Finally, after reviewing all of the evidence using the criteria for causality, the US Surgeon General's report found that overall the evidence is inconsistent and concluded that the data is suggestive, but not sufficient to infer a causal association between SHS exposure and breast cancer.

Since the 2006 US Surgeon General's report, three new case-control studies examining the association between SHS and breast cancer have been identified. A large population-based case-control study in Poland (2386 cases and 2502 controls) examining the associations between active and passive smoking and risk of breast cancer was conducted (Lissowska *et al.*, 2006). Never smoking women ever exposed to SHS at home or at work did not have a significantly elevated risk of breast

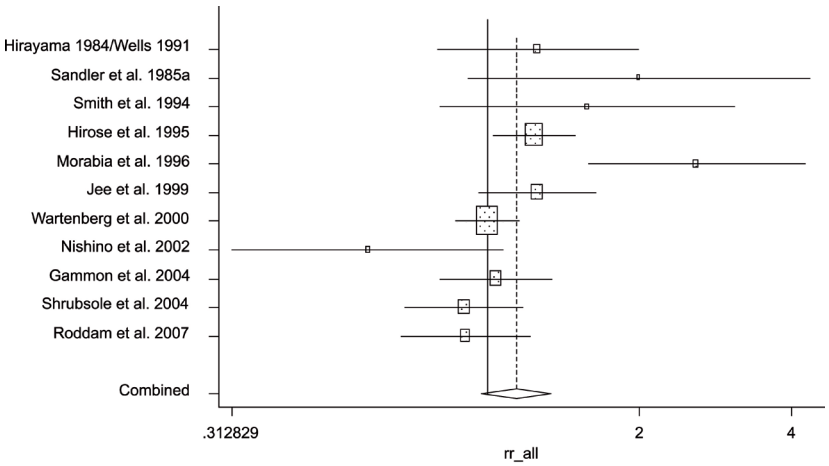


Figure 2.2a Pooled risk estimates from random effects meta-analysis of exposure to SHS from spouse and breast cancer in all women

cancer (OR=1.10; 95% CI=0.84-1.45). In addition, a trend was not observed between increasing hours/day-years of SHS and risk of breast cancer (*p for trend*=0.24) (Lissowska *et al.*, 2007). A population-based case-control study of breast cancer in women aged 36-45 years (639 cases and 640 controls) was conducted. Among never smoking women, there was no significant association between SHS exposure from a partner in the home and risk of breast cancer (RR=0.89; 95% CI=0.64-1.25). Additionally, there was not a trend with increasing duration of SHS exposure (p=0.31) and heterogeneity of the association comparing pre- and postmenopausal women (p=0.35) (Roddam *et al.*, 2007). The association between SHS and risk of breast cancer was evaluated in non-Hispanic white (NHW) and Hispanic/American Indian (HAI) women from the Southwestern USA (1527 NHW and 798 HAI cases; 1601 NHW and 924 HAI controls) (Slattery *et al.*, 2008). Among never smokers, exposure to SHS only increased the odds of premenopausal breast cancer in HAI women (OR=2.3; 95% CI=1.2-4.5). In addition, HAI premenopausal never smoking women with the rs2069832 IL6 GG genotype exposed to ≥10 hours of SHS per week, compared to those with no SHS exposure, had over four times the odds of breast cancer (OR=4.4; 95% CI=1.5-12.8, *p for interaction*=0.01).

The meta-analysis of SHS exposure and breast cancer risk in the 2006 US Surgeon General's report on involuntary smoking, was updated for this Handbook to include the three new case-control studies identified by literature search. Since many of the studies provided risk estimates that were stratified by mutually exclusive exposure categories, these estimates were pooled using random effects meta-analysis. Risk estimates were then also pooled across studies using random effects meta-analysis (Table 2.5; Figures 2.2a-c). Pooled estimates were calculated for three population samples: all women in a study (regardless of menopausal status), premenopausal women, and post-menopausal women. Three exposure categories were considered: spouse/partner in adulthood, adulthood work exposure, and childhood parental exposure in the home.

For all women, the updated, combined relative risk from exposure from a spouse or partner was 1.14 (95% CI=0.97-1.34, *p for heterogeneity*=0.002), slightly smaller than the US Surgeon General's report's combined estimate of 1.18 (95% CI=0.99-1.39, *p for heterogeneity*=0.002). The updated, combined estimate used the pooled (random effects) results for duration of exposure to SHS from a partner in never smoking women aged 36-45 years (RR=0.91; 95% CI=0.67-1.22) (Roddam *et al.*, 2007). The combined RR for all women from occupational SHS exposure was 1.10 (95% CI=0.88-1.38, *p for heterogeneity*=0.004), slightly larger than the US Surgeon General's report's combined estimate of 1.06 (95% CI=0.84-1.35, *p for heterogeneity*=0.008). No new data were available for updating estimates for childhood parental SHS exposures since the 2006 US Surgeon General's report. The Begg's and Egger's tests provided evidence for publication bias in studies among all women for occupational SHS exposure during adulthood.

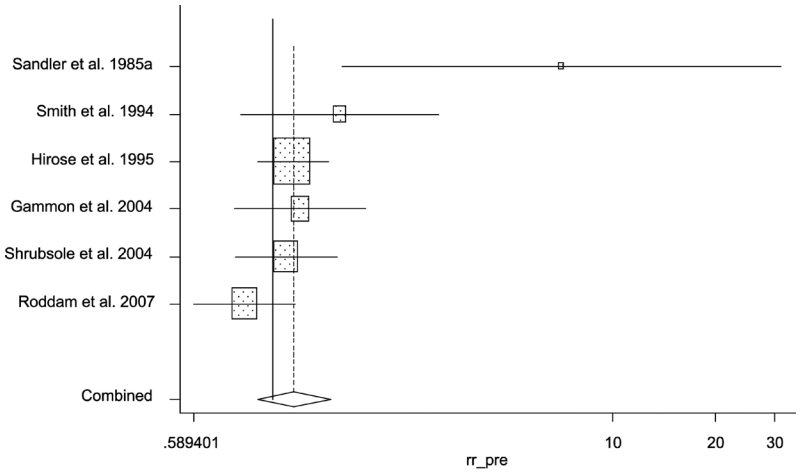


Figure 2.2b Pooled risk estimates from random effects meta-analysis of exposure to SHS from spouse and breast cancer in premenopausal women

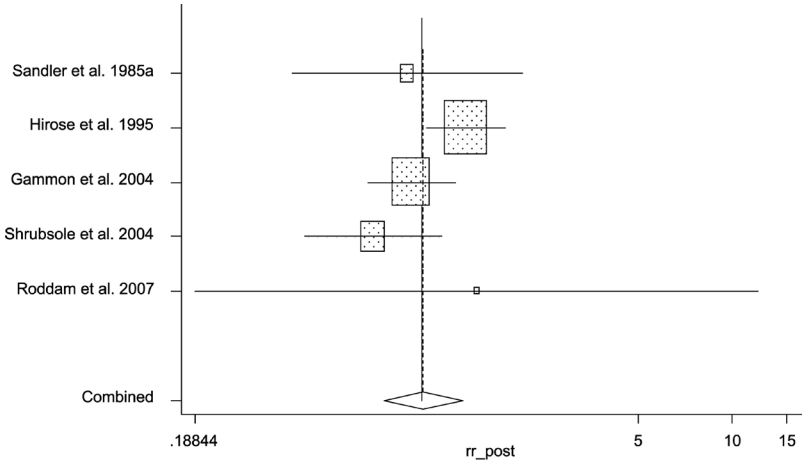


Figure 2.2c Pooled risk estimates from random effects meta-analysis of exposure to SHS from spouse and breast cancer in postmenopausal women

Updated combined estimates from this meta-analysis were also calculated for studies stratified by menopausal status. For premenopausal women, the updated combined relative risk from exposure from a spouse or partner was 1.16 (95% CI=0.91-1.48, *p for heterogeneity*=0.074), slightly smaller than the US Surgeon General's report's combined estimate of 1.25 (95% CI=0.97-1.62, *p for heterogeneity*=0.164). Among postmenopausal women, the updated combined relative risk from exposure from a spouse or partner was 1.02 ((95% CI=0.76-1.36), *p for heterogeneity*=0.143), almost the same as the US Surgeon General's report's combined estimate of 1.00 (95% CI=0.73-1.38, *p for heterogeneity*=0.080). These updated combined estimates include results from Roddam *et al.* (2007). No new data were available, since the 2006 US Surgeon General's report, for updating combined estimates for pre- and postmenopausal women's workplace or childhood SHS exposures. The Begg's and Egger's tests did not provide evidence of publication bias for studies among premenopausal women for SHS exposure from spouse or partner.

The results for the relationship between SHS exposure and breast cancer risk from this meta-analysis diverge from those of the 2005 California EPA report on environmental tobacco smoke. In addition to inclusion of the recently published studies contained in this Handbook, the selection of studies included in the California EPA meta-analyses is a likely explanation for this difference.

Table 2.5 Random effects meta-analysis results of SHS and breast cancer (2006 US Surgeon General's report and updated estimates by Volume 13 Working Group)

	All women				Premenopausal				Postmenopausal			
Exposure	n	SG (2006)	n	Updated	n	SG (2006)	n	Updated	n	SG (2006)	n	Updated
Adult (spousal)	10	1.18 (0.99-1.39) [0.002]	11	1.14 (0.97-1.34) [0.002]	5	1.25 (0.97-1.62) [0.164]	6	1.16 (0.91-1.48) [0.074]	4	1.00 (0.73-1.38) [0.080]	5	1.02 (0.76-1.36) [0.143]
Adult (work)	6	1.06 (0.84-1.35) [0.008]	7	1.10 (0.88-1.38) [0.004]	4	1.21 (0.70-2.09) [0.000]	4	1.21 (0.70-2.09) [0.000]	3	0.83 (0.53-1.29) [0.086]	3	0.83 (0.53-1.29) [0.086]
Child (parental)*	9	1.01 (0.90-1.12) [0.101]	9	1.01 (0.90-1.12) [0.101]	4	1.14 (0.90-1.45) [0.339]	4	1.14 (0.90-1.45) [0.339]	3	1.04 (0.86-1.26) [0.242]	3	1.04 (0.86-1.26) [0.242]

SG: US Surgeon General
*No new studies
n: number of studies included in each analysis
[in brackets]: p-value for test of heterogeneity (null hypothesis is no heterogeneity)

Using six case-control studies judged unlikely to have missed three major sources of lifetime SHS exposure (childhood home, adulthood home, and work), the California EPA report presented a combined relative risk estimate among all women of 1.89 (95% CI=1.52-2.36, *p for heterogeneity*=0.265). The analysis, which included all 17 studies, yielded a combined relative risk among all women of 1.40 (95% CI=1.17-1.68, *p for heterogeneity*=0.0). Among studies which presented results for premenopausal women, the California EPA report presented a combined relative risk estimate from six case-control studies deemed unlikely to have missed major sources of lifetime SHS exposure to be 2.20 (95% CI=1.70-2.85, *p for heterogeneity*=0.361), while using all 11 case-control studies yielded a combined relative risk of 1.99 (95% CI=1.49-2.66).

Cervical cancer

The US Surgeon General (U.S. Department of Health and Human Services, 2006), the California EPA (California Environmental Protection Agency: Air Resources Board, 2005), and the IARC (2004) reports all addressed the relationship between SHS exposure and risk of cervical cancer. A literature search identified a total of 12 studies with 13 study samples (Tables 2.6a,b) that examined the association between exposure to SHS and cervical cancer.

Table 2.6a Exposure to SHS and cervical cancer - Cohort studies

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hirayama, 1981 Tokyo, Japan, 1966-1979	91 540 nonsmoking wives followed for 14 years	Interviewed about risk factors		**RR (90% CI)**		
			Husband nonsmoker	1		
			Husband ex-smoker or 1-19 cig/day	1.15		
			Husband smokes 20+ cig/day	1.14		
			p for trend	0.249		
Hirayama, 1984 Tokyo, Japan 1966-1981	91 540 nonsmoking wives followed for 16 years	Interviewed about risk factors		**RR (90% CI)**	Age by Mantel-Haenszel method	
			Husband nonsmoker	1		
			Husband smokes 1-14 cig/day	1.67 (0.67-4.20)		
			Husband smokes 15-19 cig/day	2.02 (0.64-6.33)		
			Husband smokes 20+ cig/day	2.55 (1.04-6.27)		
			p for trend	0.0248		
Jee *et al*., 1999 Korea 1994-1997	Korean women aged 40-88 who received health insurance from KMIC	Questionnaires from 1992, 1993, and 1994 conducted in 416 hospitals	Husband's smoking status		Age of wives and husbands, SES, residency, husband's vegetable consumption, husband's occupation	
			Husband never smoker	1.0		
			Husband ever smoked	0.9 (0.6-1.3)		
			Husband current smoker	0.9 (0.6-1.2)		
Nishino *et al*., 2001 Japan 1984-1993	9675 Japanese lifelong nonsmoking women	Self-administered questionnaire completed in 1984	Husband nonsmoker	1.0		
			Husband smokes	1.1 (0.26-4.5)		
			p value	0.925		

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Tay & Tay, 2004 Singapore 1995-2001	623 women attending colposcopy clinic for evaluation between 1995 and 2001			**OR (95% CI)**	Age, parity, age at first intercourse, birth control pill use, patients smoking	Not restricted to never smokers
			Husband nonsmoker	1		
			LSIL: Husband smokes 1 more cig/day	1.03 (0.990-1.071)		LSIL: Low grade squamous intra-epithelial lesion
			HSIL: Husband smokes 1 more cig/day	1.046 (1.013-1.080)		HSIL: High grade squamous intraepithelial lesion
Trimble *et al.*, 2005 Washington County, MD, 1963-1978	Female residents of Washington County, MD who agreed to participate in original cohorts	Mailed questionnaires and door-to-door interviews	No Passive Smoking (PS)	1.0	Age	Analysis among Never smokers. PS refers to passive smoking
			PS only	2.5 (1.3-3.3)		
			Other household member	2.6 (1.6-4.0)		
			Spouse	2.2 (1.2-4.3)		
			Never smoker, no PS	1.0	Age, education, marital status, religious attendance	
			PS only	2.1 (1.3-3.3)		
			Other household member	2.3 (1.1-4.9)		
			Spouse	2.0 (1.2-3.3)		
Washington County, MD, 1975-1994			No PS	1.0	Age	
			PS only	1.3 (0.7-2.3)		
			Other household member	1.3 (0.7-2.5)		
			Spouse	1.6 (0.7-3.9)		
			Never smoker, no PS	1.0	Age, education, marital status, religious attendance	
			PS only	1.4 (0.8-2.4)		
			Other HH member	1.3 (0.6-3.2)		
			Spouse	1.6 (0.7-3.9)		

Table 2.6b Exposure to SHS and cervical cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Buckley *et al.*, 1981 England 1974-1979	31 husbands of married women with cervical dysplasia, carcinoma in situ, or invasive cervical cancer	62 husbands of patients without cervical dysplasia, carcinoma in situ, or invasive cervical cancer matched for age and age at first intercourse	Husbands and wives interviewed either at health clinic or at home	**Cervical dysplasia, carcinoma in situ:** husband's smoking status	RR	Matched for age and age at first intercourse	
				Nonsmoker	1		
				Ex-smoker	4.42		
				Current smoker	1.91		
				Chi-square for trend	2.42		
				Invasive carcinoma: husband's smoking status	RR	Matched for age and age at first intercourse	
				Nonsmoker	1		
				Ex-smoker	1.82		
				Current smoker	4.44		
				Chi-square for trend	2.17		
				Invasive cervical cancer: husband's smoking status	RR	Matched for age and age at first intercourse	
				Nonsmoker	1		
				Ex-smoker	2.69		
				Current smoker	3.21		
				Chi-square for trend	4.59		
Brown *et al.*, 1982 Canada 1959-1968	33 patients with invasive or in situ cervical cancer	29 with hysterectomies for non-cancer reasons	Interview using questionnaire	**Invasive cancer:** Husband nonsmoker	1	Matched for age at surgery, parity, social class, and date of surgery	Unmatched crude ORs calculated from table
				Husband smokes <20 cig/day	0.55		
				Husband smokes 20-40 cig/day	1.25		
				Husband smokes >40 cig/day	6.00		

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Brown *et al.*, 1982 Canada 1959-1968				**Total cervical cancer:** Husband nonsmoker Husband smokes <20 cig/day Husband smokes 20-40 cig/day Husband smokes >40 cig/day	 1 1.36 5.00 15.00		
Sandler *et al.*, 1985b University of North Carolina 1979-1981	All cancer cases (except basal cell skin) from North Carolina Memorial Hospital tumor registry diagnosed between 1979 and 1981 and alive in 1981; aged 15-59	Friends or acquaintances of case without cancer, of similar age (±5 yrs), sex, and race, or through telephone sampling	Mailed questionnaire and telephone call	Mother nonsmoker Mother smoked Father nonsmoker Father smoked	1 0.77 1 1.7	None	Results presented among nonsmokers; CIs not presented
Sandler *et al.*, 1985a University of North Carolina 1979-1981	All cancer cases (except basal cell skin) from North Carolina Memorial Hospital tumor registry diagnosed between 1979 and 1981 and alive in 1981; aged 15-59	Friends or acquaintances of case without cancer, of similar age (+/- 5 yrs), sex, and race, or through telephone sampling	Mailed questionnaire and telephone call	Spouse did not smoke Spouse smoked	1 2.1 (1.2-3.9)		Results among nonsmokers presented
Hellberg *et al.*, 1986 Falu Hospital, Sweden 1977-1981	140 pregnant women histologically diagnosed with cervical intraepithelial neoplasia using colposcopy	280 pregnant age-matched women (2 for each case) also visiting the maternity clinic on the same occasion with normal smears	Midwife administered questionnaire and mailed it	Male partner nonsmoker Male partner smokes *p value*	1 2.01 (1.84-2.21) <0.001		Unmatched OR calculated from table
Slattery *et al.*, 1989 Utah 1984-1987	266 histologically confirmed incident cases of carcinoma in situ or invasive carcinoma identified through rapid reporting system	408 age- and residence-matched controls using random digit dialing sampling without history of hysterectomy before 1984 or missing data	Personal interviews in respondents' homes	No hrs/day of passive smoking (PS) 0.1-0.9 hrs/day 1.0-2.9 hrs/day ≥3.0 hrs/day of	1 1.14 (0.45-2.94) 1.57 (0.52-4.73) 3.43 (1.23-9.54)	Age, education, church attendance, # sexual partners of woman; age and residence matched	Results among never smokers presented (81 cases and 305 controls). PS refers to passive smoking

Table 2.6b Exposure to SHS and cervical cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Slattery *et al.*, 1989 Utah 1984-1987				**No hrs/day of PS in-home**	1		
				0.1-1.5 hrs/day	0.62 (0.25-1.53)		
				>1.5 hrs/day	2.66 (1.15-6.13)		
				No hrs/day of PS away from home	1		
				0.1-1.5 hrs/day	1.33 (0.58-3.07)		
				>1.5 hrs/day	2.3 (0.89-5.95)		
				None in-home PS	1		
				Little in-home PS	1.86 (0.37-9.37)		
				Some in-home PS	1.49 (0.44-5.09)		
				A lot in-home PS	2.93 (1.08-7.94)		
				None away from home PS	1		
				Little away from home PS	1.58 (0.68-3.66)		
				Some away from home PS	1.11 (0.49-2.50)		
				A lot away from home PS	1.59 (0.57-4.45)		
Coker *et al.*, 1992 University of North Carolina 1987-1988	103 cases with CIN grades II and III; aged 18-45 years; Black or White and non-pregnant; response rate 92%	268 normal controls; aged 18-45 years; black or white and non-pregnant; response rate 91.8%	Interviewed by telephone or in person	**No PS at home**	1	Age, race, education, # sex partners, # Paps in last 5 yrs, genital warts	Results for nonsmoking women
				<17 yrs at home	1.5 (0.5-4.9)		
				18+ yrs at home	0.4 (0.1-1.3)		
				No PS at work	1		
				1-4 yrs at work	1.7 (0.5-5.1)		
				5+ yrs at work	0.4 (0.1-2.5)		
				Not exposed	1		
				Parent only	0.4 (0.1-1.2)		

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Coker *et al.*, 1992				Husband only	1.5 (0.3-6.2)		
University of North Carolina 1987-1988				Parent and husband	0.4 (0.1-1.9)		
				Others only	1.8 (0.4-8.4)		
Hirose *et al.*, 1996	556 women with first diagnosis, histologically confirmed cervical cancer	26 751 first visit outpatients aged ≥20 without ever being diagnosed with cancer	Self-administered questionnaire		AOR (95% CI)	Age, first-visit year, drinking, physical activity	Results for nonsmoking women
Aichi Cancer Center, Japan 1996				Husband nonsmoker	1		
				Husband smokes	1.3 (1.07-1.59)		
				Husband smokes <20 cig/day	1.0 (0.76-1.33)		
				Husband smokes ≥20 cig/day	1.55 (1.24-1.94)		
Coker et al., 2002	High-grade SIL (HSIL) cases, 313 low-grade SIL (LSIL) cases, with mean age near 25 years; response rate 82.1%	427 controls with mean age near 28 years; response rate 72.5%	Interviewed by telephone	**HSIL:** No passive smoking (PS) by either parent/ sex partner	1	Age, age at first sexual intercourse, race, HR-HPV status, and active smoking	Not restricted to nonsmokers. High grade squamous intraepithelial lesion.
South Carolina Health Department, 1995-1998				PS by either parent/ sex partner	2.2 (1.0-4.8)		
				No PS by parent as a child	1		
				PS by parent as a child	1.9 (1.0-3.7)		
				No PS by sex partner	1		
				PS by sex partner	1.0 (0.5-2.1)		
				No PS	1		
				1-9 yrs of PS	0.7 (0.2-2.6)		
				10+ yrs of PS	1.8 (0.9-3.6)		
				LSIL: No PS by either parent or sex partner	1		Low grade squamous intraepithelial lesion
				PS by either parent or sex partner	1.4 (1.0-2.0)		PS refers to passive smoking

Table 2.6b Exposure to SHS and cervical cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Coker *et al.*, 2002 1995-1998				No PS by parent as a child	1		
				PS by parent as a child	1.2 (0.9-1.7)		
				No PS by sex partner	1		
				PS by sex partner	1.1 (0.8-1.5)		
				Never PS	1		
				1-9 yrs of PS	1.8 (1.1-3.0)		
				10+ yrs of PS	1.4 (0.9-2.0)		
Wu *et al.*, 2003 Taiwan 1999-2000	100 histologically confirmed women (CIN2: 39, CIN3:12, CIS: 46, invasive cancer: 3) aged ≥19	197 women age (±2 yrs) and residence matched with negative Pap smears	Nurse interviewer-administered questionnaire	No childhood, home ETS exposure	1	Age and residence-matched, education, # pregnancies, age at first intercourse, cooking ventilation	Results for nonsmoking women ETS refers to environmental tobacco smoke ETS refers to environmental tobacco smoke
				Childhood, home ETS exposure	0.99 (0.54-1.83)		
				No childhood, work ETS exposure	1		
				Childhood, work ETS exposure	1.03 (0.47-2.26)		
				No adulthood, home ETS exposure	1		
				Adulthood, home ETS exposure	2.73 (1.31-5.67)		
				No adulthood, work ETS exposure	1		
				Adulthood, work ETS exposure	1.56 (0.83-2.92)		
				Lifetime, childhood, home ETS exposure			
				No	1		
				1-10 cig/day	1.35 (0.78-2.35)		
				>10 cig/day	1.02 (0.43-2.40)		

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Wu *et al.*, 2003				Lifetime, childhood, work ETS exposure			
Taiwan 1999-2000				No	1		
				1-10 cig/day	1.25 (0.54-2.90)		
				>10 cig/day	0.79 (0.24-2.55)		
				Lifetime, childhood, home ETS exposure			
				No	1		
				1-10 cig/day	1.11 (0.59-2.09)		
				>10 cig/day	0.82 (0.31-2.19)		
				Lifetime, childhood, work ETS exposure			
				No	1		
				1-10 cig/day	1.34 (0.53-3.36)		
				>10 cig/day	0.79 (0.21-2.97)		
				Lifetime, adulthood, home ETS exposure			
				No	1		
				1-10 cig/day	2.13 (0.96-4.73)		
				>10 cig/day	3.97 (1.65-9.55)		
				Lifetime, adulthood, work ETS exposure			
				No	1		
				1-10 cig/day	1.47 (0.64-3.37)		
				>10 cig/day	1.65 (0.73-3.75)		
				Lifetime, adulthood, all ETS exposure			
				No	1		
				1-10 cig/day	1.90 (0.72-5.03)		
				>10 cig/day	2.99 (1.10-8.09)		

Table 2.6b Exposure to SHS and cervical cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Sobti *et al.*, 2006 India	103 histologically confirmed cervical cancer patients	103 controls free of any cancer	Interviewer-administered questionnaire	**GSTM1 null:** Never smoker Passive smoker	 1 6.95		ORs calculated from table
				GSTM1 present: Never smoker Passive smoker	 1 4.32		GSTM1 gene (glutathione S-Transferese mu1)
				GSTT1 null: Never smoker Passive smoker	 1 28.57		GSTT1 (glutathione S-transferese theta1)
				GSTM1 present: Never smoker Passive smoker	 1 3.72		
				GSTP1 ile/ile: Never smoker Passive smoker	 1 4.33		
				GSTP1 ile/val: Never smoker Passive smoker	 1 5.53		GSTP1 gene (glutathione S-transferese pi1)
				GSTP1 val/val: Never smoker Passive smoker	 1 5.13		
Tsai *et al.*, 2007 Taiwan 2003-2005	Women aged ≥20 screened by PAP smear with CIN I or over for the first time	Randomly selected from women with negative Pap smear findings, matched on residence and agreeing to interview	Interviewer-administered questionnaire	**Inflammation:** Non-smoker	1	Age, education, times of prior Pap smear, # of lifetime sexual partners, age at first intercourse, family history cervical cancer, cooking oil fume exposure, HPV infection	Results for nonsmoking women
				Secondhand smoker	1.3 (0.6-2.7)		
				Nonsmoker	1		
				Lifetime 1-10 pack/yrs	0.9 (0.4-1.9)		
				Lifetime 11-20 pack/yrs	1.7 (0.5-5.6)		
				Lifetime >20 pack/yrs	4.1 (1.3-12.5)		
				CIN1: Nonsmoker	1		CIN (Cervical Intra-epithelial neoplasia grade 1)
				SHS	1.6 (0.8-3.2)		
				Nonsmoker	1		

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Tsai *et al.*, 2007 Taiwan 2003-2005				Lifetime 1-10 pack/yrs	1.3 (0.6-2.8)		
				Lifetime 11-20 pack/yrs	2.4 (0.7-7.7)		
				Lifetime >20 pack/yrs	4.0 (1.2-13.8)		
				≥CIN2: Nonsmoker	1		CIN2 (Cervical Intra-epithelial neoplasia grade 2)
				Secondhand smoker	1.8 (0.9-4.1)		
				Nonsmoker	1		
				Lifetime 1-10 pack/yrs	1.3 (0.6-2.9)		
				Lifetime 11-20 pack/yrs	2.1 (0.6-7.9)		
				Lifetime >20 pack/yrs	7.2 (2.5-20.6)		

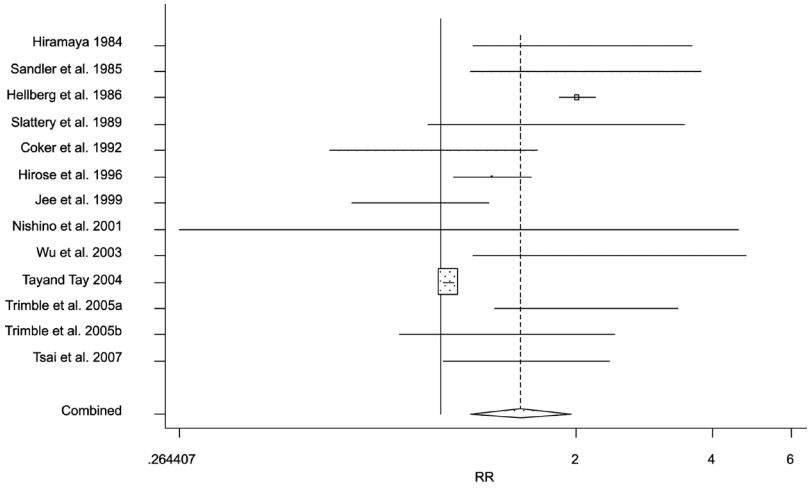


Figure 2.3 Pooled risk estimates from random effects meta-analysis of exposure to SHS and cervical cancer

Trimble et al., 2005a and 2005b refer to estimates from the 1963 and 1975 cohorts respectively. All data included in the reference Trimble et al., 2005

Risk estimates are plotted in Figure 2.3 for the most comprehensive SHS exposure index available. Since several studies presented risk estimates stratified by mutually exclusive exposure categories (Hirayama, 1984; Slattery *et al.*, 1989; Coker *et al.*, 1992; Hirose *et al.*, 1996; Wu *et al.*, 2003; Tay & Tay, 2004; Tsai *et al.*, 2007), these estimates were pooled using random effects meta-analysis. Although a combined random effects estimate is shown, none of these studies adequately accounted for prior human papillomavirus (HPV) infection. Consequently, the evidence is not informative as to whether SHS increases the risk of cervical cancer in HPV-infected women. Overall, increased risk was found in association with SHS exposure (Figure 2.3). However, the increase cannot be separated from increased risk for HPV infection indirectly associated with SHS exposure.

Colorectal cancer

Several recent studies, addressing genetic markers of risk, have examined the relationship between passive smoking and colorectal cancer. It was found that passive smoking was associated with an increased risk for colorectal cancer only among NAT2 fast acetylators (OR=2.6; 95% CI=1.1-5.9) for exposure in childhood and adulthood (Lilla *et al.*, 2006). After adjusting for active smoking, total long-term exposure to passive smoke was found to be associated with increased risk of rectal cancer among men exposed to >10 hours/week compared to none (OR=1.4; 95% CI=1.0-2.1), but no significant associations were found between exposure to SHS and rectal cancer among women (Slattery *et al.*, 2003).

Esophageal cancer

This review identified one published study examining the relationship between SHS exposure and esophageal cancer (Wang *et al.*, 2006). The researchers conducted a population based case-control study in 107 esophageal squamous cell carcinoma cases and 107 controls matched on residency, age, and sex in five townships of Huaian, China. They found that exposure to SHS was associated with an increased risk of esophageal cancer (OR=2.04; 95% CI=1.14-3.70). However, these results were not restricted to nonsmokers.

Liver cancer

The relationship between passive smoking and risk for cancer of the liver has also been investigated. A prospective cohort study conducted in 160 130 Korean women, aged 40-88, found no association between liver cancer and husbands' smoking habit (Jee *et al.*, 1999). There were 83 cases of liver cancer identified in the follow-up period from July, 1994 to December, 1997. Wives with former smoking husbands had RR=0.8 (95% CI=0.5-1.5) and wives of current smoking husbands had RR=0.7 (95% CI=0.4-1.1). Another cohort study conducted in Japanese nonsmoking women, found an elevated, but not significant, age-adjusted risk of liver cancer after nine years of follow-up (OR=1.2; 95% CI=0.45-3.2) (Nishino *et al.*, 2001); however, there were only 20 cases of liver cancer. It was hypothesised

that parental smoking during pregnancy might plausibly increase risk for childhood hepatoblastoma by exposing the fetus' liver through the fetal circulation (Pang *et al*., 2003). Though there were only 10 cases, they found a significantly elevated OR of developing hepatoblastoma associated with smoking by both parents (OR=4.74; 95% CI=1.68-13.35). An increased risk of hepatoblastoma was also reported if both parents smoked relative to neither parent smoking (RR=2.28; 95% CI=1.02-5.09) (Sorahan & Lancashire, 2004).

Lymphoma

Only one study has been published examining the relationship between SHS exposure and cancer of the lymph nodes in adults. A population-based case-control study was conducted examining the association between SHS exposure and Hodgkin lymphoma (HL) among US women aged 19-44 years and those aged 45-79 years (Glaser *et al*., 2004). Though not limited to never smokers, exposure to SHS during childhood was significantly associated with risk of HL in the 19-44 year age group (OR=1.6; 95% CI=1.03-2.4) after adjusting for age, race, having a single room at 11 years, birth place (USA vs. other), renting a house/dwelling at age eight, being Catholic, and ever breastfeeding. Exposure to SHS during adulthood was not significantly associated with risk of HL (adjusted OR=0.8; 95% CI=0.6-1.2).

Nasal sinus cancer

The 2006 Surgeon General's report on involuntary smoking addressed SHS exposure and risk of nasal sinus cancer. Only three studies were found (Hirayama, 1984; Fukuda & Shibata, 1990; Zheng *et al*., 1993) with up to a three-fold increase in nasal sinus cancer risk associated with SHS exposure (Tables 2.7a,b). The report concluded that the evidence regarding SHS exposure and nasal sinus cancer was suggestive, but not sufficient to infer a causal relationship, and that more studies by histological type and subsite were needed. New studies were not found.

Nasopharyngeal cancer

The 2006 US Surgeon General's report on involuntary smoking also addressed SHS exposure and the risk of nasopharyngeal cancer. Only three studies were found in the literature (Yu *et al*., 1990; Cheng *et al*., 1999; Yuan *et al*., 2000) showing slightly elevated related relative risks. The US Surgeon General's report concluded that though biologically plausible, the evidence regarding SHS exposure and nasopharyngeal cancer was inadequate to infer a causal relationship. Since this review, no new studies have been published in the literature regarding SHS exposure and risk of nasopharyngeal cancer (Table 2.8).

Oral cancer

Few studies have examined the role of SHS in the etiology of oral cancer. In a case-control study of overall cancer and adult exposure to passive smoking, it was found that exposure to passive smoke was not significantly associated with cancer of the lip, oral cavity, and pharynx after adjusting for age and education (OR=1.1; 95% CI=0.4-3.0) (Sandler *et al*., 1985a). Another case-control study found that neither exposure to maternal nor paternal smoking during childhood was associated with an unadjusted risk of cancer of the lip, oral cavity, and pharynx (maternal smoking OR=0.8; 95% CI=0.2-3.5, paternal smoking OR=1.3; 95% CI=0.4-3.8) (Sandler *et al*., 1985b). Neither of these studies was limited to never smokers.

Ovarian cancer

A cohort study conducted in Japanese nonsmoking women, found an elevated, but not significant, increased risk of ovarian cancer associated with husbands smoking status after adjusting for age (OR=1.7; 95% CI=0.58-5.2) (Nishino *et al*., 2001). However, there were only 15 cases of ovarian cancer reported during nine years of follow-up for 9675 women. A population-based case-control study in the USA, examined the hypothesis that active and passive tobacco smoking are associated with the risk of epithelial ovarian cancer (558 women with epithelial ovarian cancer and 607 population controls) (Goodman & Tung, 2003). Significant associations were not found among never smokers with exposure to passive smoke from either parent for gestational or childhood exposure. In a study among never smokers (434 cases and 868 age and region matched hospital controls), a decreased risk of ovarian cancer was found to be associated with daily exposure to passive smoke (OR=0.68; 95% CI=0.46-0.99) (Baker *et al*., 2006).

Table 2.7a Exposure to SHS and nasal sinus cancer - Cohort study

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders
Hirayama *et al.*, 1984	91 540 nonsmoking, married women, aged ≥40 years (28 deaths due to nasal sinus cancer)	Interviewer-administered questionnaire	Husband's smoking:	RR (90% CI)	Husband's age
Japan 1966-1981			None	1	
			1-14 cig/day	1.67 (0.67-4.20)	
			15-19 cig/day	2.02 (0.64-6.33)	
			≥ 20 cig/day	2.55 (1.04-6.27)	

Table 2.7b Exposure to SHS and nasal sinus cancer - Case-control study

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI) or odds ratio	Adjustment for potential confounders
Fukuda & Shibata, 1990	46 women 40-79 years with incident neoplasms of the maxillary sinuses; 96.6% response rate	88 population controls, individually matched on age, gender, and health-center region; 93.4% response rate	Self-administered questionnaire	**Among nonsmokers:**		none
Japan 1982-1986				No smokers in household	1	
				1 smoker in household	1.40 (0.57-3.49)	
				>1 smoker in household	5.73 (1.58-20.73)	
Zheng *et al.*, 1993	147 deaths from nasal sinus cancer in White males aged ≥45 years who participated in the 1986 US National Mortality Followback Survey	449 White controls aged ≥45 years who died from other causes	Questionnaire sent to next of kin	Nonsmoker in household	1	
USA 1986				Smoking spouse	3.0 (1.0-8.9)	age, alcohol
				Smoking spouse, maxillary sinus cancers	4.8 (0.9-24.7)	age, alcohol

Table 2.8 Exposure to SHS and nasopharyngeal cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders
Yu *et al.*, 1990 China 1983-1985	306 patients <50 years old with incident nasopharyngeal carcinoma; 100% response rate	306 population controls, individually matched on age, gender, and neighborhood; response rate not stated	Interviewer-administered questionnaire	**Among nonsmokers:** Never exposed to SHS at home Father smoked when subject was age 10 Mother smoked when subject was age 10 Other household members smoked when subject was age 10 Lived with any smoker at age 10 Spouse smoked Ever exposed to SHS at home	 1 0.6 (0.3-1.2) 0.7 (0.3-1.5) 1.0 (0.5-2.2) 0.7 (0.4-1.3) 0.8 (0.4-1.9) 0.7 (0.4-1.4)	Age and gender
Cheng *et al.*, 1999 Taiwan 1991-1994	375 histologically confirmed incident nasopharyngeal cancers (NPC),≤75 years old, no previous NPC, residence in Taipei last 6 months; 99% response rate	327 healthy community controls individually matched to cases on sex, age and residence; 88% response rate	Questionnaire	**Nonsmokers**: No childhood SHS Childhood SHS No adulthood SHS Adulthood SHS	 1 0.6 (0.4-1.0) 1 0.7 (0.5-1.2)	Age, sex, education, family history of NPC
Yuan *et al.*, 2000 China 1987-1991	935 histologically confirmed nasopharyngeal cancers; 84% response rate	1032 persons from the community frequency matched by age (± 5 yrs) and sex	In-person interview by 4 trained interviewers employing a structured questionnaire	**Male and female nonsmokers:**		Age, sex, education, preserved foods, citrics, cooking smoke, occupational exposure to chemical fumes, history of chronic ear, nose condition, family history of NPC

Table 2.8 Exposure to SHS and nasopharyngeal cancer - Case-control studies

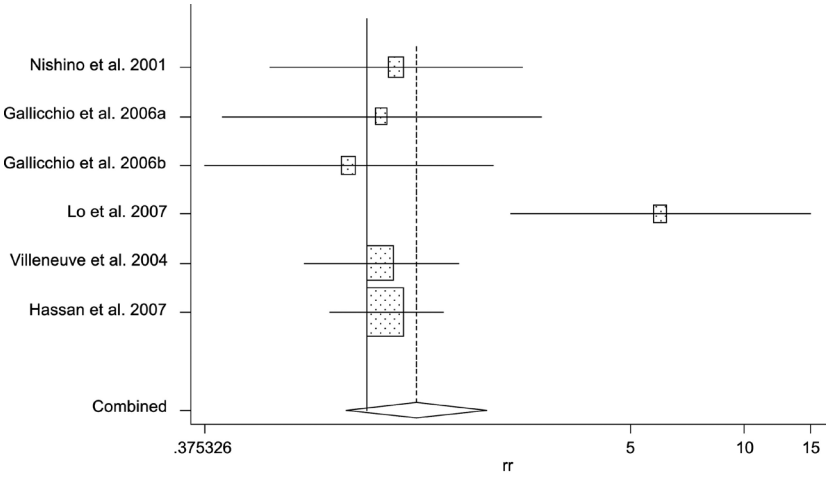
Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders
Yuan *et al.*, 2000 China 1987-1991				Never exposed over lifetime	1	
				Mother smoked	2.30 (1.23-4.28)	
				Mother smoked <20 cig/day	1.65 (0.83-3.29)	
				Mother smoked ≥20 cig/day	4.24 (1.84-9.77)	
				Father smoked	1.99 (1.18-3.35)	
				Father smoked <20 cig/day	1.73 (0.99-3.02)	
				Father smoked ≥20 cig/day	2.28 (1.31-3.99)	
				Non-parental household member smoked	2.37 (1.20-4.71)	
				Any household member smoked	2.05 (1.22-3.44)	
				Total household <20 pack-yrs	1.78 (1.02-3.13)	
				Total household 20-39 pack-yrs	2.23 (1.28-3.89)	
				Total household 40+ pack-yrs	2.51 (1.18-5.34)	
				Spouse smoked	2.48 (1.42-4.31)	
				Spouse smoked <20 yrs	2.37 (1.28-4.41)	
				Spouse smoked 20+ yrs	2.59 (1.38-4.84)	
				Spouse smoked <20 cig/day	2.44 (1.35-4.42)	
				Spouse smoked 20+ cig/day	2.52 (1.36-4.65)	
				Spouse <20 pack-yrs	2.47 (1.37-4.45)	

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders
Yuan *et al.*, 2000				Spouse 20-39 pack-yrs	2.12 (1.07-4.19)	
China 1987-1991				Spouse 40+ pack-yrs	4.69 (1.60-13.70)	
				Non-spousal household member smoked	1.86 (1.09-3.18)	
				Any household member smoked	1.88 (1.12-3.16)	
				Total household smoked <20 cig/day	1.81 (1.03-3.19)	
				Total household smoked 20-39 cig/day	1.70 (0.97-2.98)	
				Total household 40+ cig/day	2.72 (1.39-5.31)	
				Co-worker smoked	1.99 (1.19-3.32)	
				Co-worker smoked <3 hrs	1.76 (1.03-3.02)	
				Co-worker smoked 3+ hrs	2.28 (1.32-3.93)	

The authors hypothesised that immunosuppression by nicotine or upregulation of enzymes that metabolise carcinogens may be responsible for the protective effects observed.

Pancreatic cancer

For pancreatic cancer, the literature review identified both cohort and case-control studies (Tables 2.9a,b). The three cohort studies provided no evidence for increased risk of pancreatic cancer associated with the exposure indicators (Nishino *et al.*, 2001; Gallicchio *et al.*, 2006). The case-control studies also provided little evidence for increased risk, except for one study carried out in Egypt (Lo *et al.*, 2007). This hospital-based case-control study used two institutions to identify the cases and drew controls from the otolaryngology and ophthalmology inpatient services; most cases did not have histological confirmation and there is concern about the comparability of cases and controls, given the methods of recruitment. The pooled estimate calculated by the Working Group for exposure at home as an adult was OR=1.35 (95% CI=0.88-2.07) (Figure 2.4).



Figures 2.4 Pooled risk estimates from random effects meta-analysis of exposure to SHS and pancreatic cancer

Gallicchio et al., 2006a and 2006b refer to estimates from the 1963 and 1975 cohorts respectively.
All data included in the reference Gallicchio et al., 2006

Stomach cancer

The relationship between exposure to SHS and cancer of the stomach has been investigated in five study populations (Tables 2.10a,b). In a cohort of 91 540 nonsmoking Japanese women ≥40 years, followed from 1966 to 1981, there were 854 cases of stomach cancer (Hirayama, 1984). Husband's smoking was not significantly associated with risk of stomach cancer; the ORs associated with husband being an ex-smoker or of smoking 1-19 cigarettes/day was 1.03 (90% CI=0.89-1.18) and for 20+ cigarettes/day, OR=1.05 (90% CI=0.89-1.24). Another prospective cohort study conducted in Korean women aged 40-88 years, examined the association between SHS exposure from the husband's smoking and risk of stomach cancer (Jee *et al.*, 1999). It was found that neither husband's former smoking (OR=1.0; 95% CI=0.7-1.5) nor current smoking (OR=0.9; 95% CI=0.6-1.2) were associated with risk of stomach cancer in their wives. Also examined was the association between SHS and stomach cancer in a population-based prospective study among Japanese women aged 40 years and older during nine years of follow-up (Nishino *et al.*, 2001). The age-adjusted RR for stomach cancer associated with husband's smoking was 0.95 (95% CI=0.58-1.6).

Two case-control studies examined the relationship between SHS exposure and risk of stomach cancer. Using information on 65 incident stomach cancer cases and 343 population controls, identified between 1994 and 1997 in Canada, it was found that among male never smokers there was a strongly increased risk associated with residential and occupational exposure to SHS among subjects with cardial stomach cancer (Mao *et al.*, 2002). For men with cardial cancer, the ORs ranged from 2.5 (95% CI=0.5-13.1) for 1-55 lifetime person-years of exposure, to OR=4.5 (95% CI=0.9-21.8) for 56-125 lifetime

Table 2.9a Exposure to SHS and pancreatic cancer - Cohort studies

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Nishino *et al.*, 2001 Japan 1984-1992	9675 never smoking married women ≥40 years at enrollment (19 pancreatic cancer cases) with no previous diagnosis of cancer	Self-administered questionnaire	Husband does not smoke Husband smokes	1 1.2 (0.45-3.2)	Age	
Gallicchio *et al.*, 2006 Maryland, USA 1963-1978	18 839 never smoking adults ≥25 years at enrollment (22 pancreatic cancer cases) with no prior cancer diagnosis	Self-administered questionnaire	No household members smoke Any household member smokes	1 1.1 (0.4-2.8)	Age, education, marital status	Two separate cohort studies described in this article; men excluded from SHS exposure analyses
Maryland, USA 1975-1994	20 181 never smoking adults ≥25 years at enrollment (34 pancreatic cancer cases) with no prior cancer diagnosis	Self-administered questionnaire	No household members smoke Any household member smokes	1 0.9 (0.4-2.3)	Age, education, marital status	Two separate cohort studies described in this article; men excluded from SHS exposure analyses

person-years of exposure to SHS, after controlling for 10 year age group; province; education; social class; and meat, fruit, vegetable, and juice consumption. Among never smoking men, the adjusted ORs were lower for the distal subsite of stomach cancer than cardia. In a case-control study based in the USA, it was found that the unadjusted RR for digestive cancer associated with father's smoking was 1.7 (95% CI=0.8-3.9), and for maternal smoking, RR=0.6 (95% CI=0.2-2.1) (Sandler *et al.*, 1985b). In the same study population, the researchers found the RR for digestive cancer associated with spousal smoking to be 1.0 (95% CI=0.5-2.2) after adjusting for age and education (Sandler *et al.*, 1985a).

Childhood cancers

Childhood leukemia

The 2006 US Surgeon General's report on SHS summarised the evidence on childhood leukemia and SHS exposure. The report concluded that the evidence was suggestive, but not sufficient to infer a causal relationship between prenatal and postnatal exposure to SHS and childhood leukemia. Since this report, three new studies have been published on SHS and risk of childhood leukemia. The relationship between parental smoking and childhood leukemia in the Northern California Childhood Leukemia Study was investigated (Chang *et al.*, 2006).

Table 2.9b Exposure to SHS and pancreatic cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk(95% CI)	Adjustment for potential confounders	Comments
Villeneuve *et al.*, 2004 Canada 1994-1997	105 never-smoking adults ≥30 years with pancreatic cancer; female response rate: 56%; male response rate: 55%	1145 adult population controls, matched on province and frequency matched on age and gender; female response rate: 71%; male response rate: 65%	Self-administered questionnaire	Never exposed to SHS	1	Age, BMI, income, province, sex	
				SHS exposure at home or work up to age 19	1.37 (0.46-4.07)		
				SHS exposure at home or work during adulthood	1.01 (0.41-2.50)		
				SHS exposure at home or work in lifetime	1.21 (0.60-2.44)		
				1-20 yrs SHS exposure at home	0.97 (0.42-2.26)		
				21-34 yrs SHS exposure at home	0.90 (0.39-2.11)		
				35+ yrs SHS exposure at home	1.43 (0.66-3.11)		
				All: 1-9 yrs SHS exposure at work	1.55 (0.68-3.56)		
				10-21 yrs SHS exposure at work	1.16 (0.49-2.74)		
				22+ yrs SHS exposure at work	1.20 (0.54-2.67)		
				SHS exposure only at home	0.97 (0.43-2.18)		
				SHS exposure only at work	1.43 (0.61-3.36)		
				1-35 yrs SHS exposure at home or work	1.33 (0.60-2.93)		
				36-56 yrs SHS exposure at home or work	1.09 (0.49-2.41)		
				57+ yrs SHS exposure at home or work	1.15 (0.54-2.47)		

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk(95% CI)	Adjustment for potential confounders	Comments
Hassan *et al.*, 2007 Texas, USA 2000-2006	735 patients with newly diagnosed, histologically-confirmed pancreatic adenocarcinoma who were English speaking US citizens	805 visitors who accompanied cancer patients (usually spouses), frequency matched on age, race, and sex	Interviewer-administered questionnaire	**Nonsmokers:** Never exposed to SHS	1	Age, sex, race, diabetes, alcohol consumption, education, state of residence, marital status	294 nonsmoking cases and 412 nonsmoking controls
				Ever exposed to SHS (childhood or adulthood)	1.1 (0.8-1.6)		
				Occasional SHS exposure during childhood	0.9 (0.5-1.6)		
				Regular SHS exposure during childhood	1.1 (0.7-1.6)		
				Occasional SHS exposure at home during adulthood	1.4 (0.7-2.5)		
				Regular SHS exposure at home during adulthood	1.03 (0.7-1.6)		
				Occasional SHS exposure at work during adulthood	0.8 (0.5-1.3)		
				Regular SHS exposure at work during adulthood	1.2 (0.7-1.9)		
				SHS exposure only during childhood	1.2 (0.7-1.9)		
				SHS exposure only during adulthood	1.3 (0.8-2.2)		
				SHS exposure during both childhood and adulthood	1.0 (0.6-1.5)		
				1-5 yrs SHS exposure during childhood	0.6 (0.2-1.7)		
				6-10 yrs SHS exposure during childhood	0.6 (0.2-1.5)		
				>10 yrs SHS exposure during childhood	1.1 (0.7-1.6)		

Table 2.9b Exposure to SHS and pancreatic cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hassan *et al.*, 2007				1-10 yrs SHS exposure during adulthood	1 (0.5-1.7)		
Texas, USA 2000-2006				11-20 yrs SHS exposure during adulthood	1.1 (0.6-2.01)		
				>20 yrs SHS exposure during adulthood	1.2 (0.8-1.9)		
				1-10 yrs SHS exposure during lifetime	0.8 (0.4-1.6)		
				11-20 yrs SHS exposure during lifetime	1.1 (0.7-1.7)		
				>20 yrs SHS exposure during lifetime	1.2 (0.8-1.8)		
Lo *et al.*, 2007	194 adults 19-90 years with newly diagnosed pancreatic cancer	194 hospital controls from the ear/nose/ throat, ophthalmology units frequency-matched on age and sex	Interviewer-administered questionnaire	**Nonsmokers:** Never lived with a smoker	1	Age, sex, rural/urban residence	41 nonsmoking cases and 97 nonsmoking controls
Egypt 2001-2004				Ever lived with a smoker, <30 yrs	6.0 (2.4-14.8)		

This case-control study included 327 acute childhood leukemia cases (281 acute lymphoblastic leukemia (ALL) and 46 acute myeloid leukemia (AML)) and 416 controls matched on age, sex, maternal race, and Hispanic ethnicity. The investigators found that maternal smoking was not associated with an increased risk of either ALL (OR=1.12; 95% CI=0.79-1.59) or AML (OR=1.00; 95% CI=0.41-2.44). The OR for AML associated with paternal preconception smoking was 3.84 (95% CI=1.04-14.17). The corresponding OR for ALL associated with paternal preconception smoking was 1.32 (95% CI=0.86-2.04).

The role of maternal alcohol and coffee consumption and parental smoking on the risk of childhood acute leukemia was investigated in a multicenter, hospital-based, case-control study in France with 280 incident cases and 288 hospitalised controls, frequency matched with the cases by age, gender, and center (Menegaux *et al.*, 2005). Significant associations of maternal smoking with ALL (OR=1.1; 95% CI=0.7-1.6) and acute non-lymphocytic leukemia (ANLL) (OR=1.0; 95% CI=0.5-2.1) were not found. Paternal smoking was also not significantly associated with risk of ALL (OR=1.1; 95% CI=0.7-1.5) or ANLL (OR=1.3; 95% CI=0.6-2.7). Another case-control study was conducted in France of coffee, alcohol, SHS, and risk of acute leukemia (Menegaux *et al.*, 2007). The researchers identified 472 cases of childhood acute leukemia (407 ALL and 62 with AML) and frequency-matched 567 population controls by age, sex, and region of residence. Only the risk of ALL associated with maternal smoking

during pregnancy was significantly elevated (OR=1.4; 95% CI=1.0, 1.9), after adjusting for age, gender, region, socio-professional category, and birth order. Paternal smoking before, during, or after pregnancy was not significantly associated with risk of either ALL or AML. These new studies provide more evidence suggesting a causal relationship between prenatal and postnatal exposure to SHS and childhood leukemia.

Childhood brain cancer

The US Surgeon General (U.S. Department of Health and Human Services, 2006), the California EPA (California Environmental Protection Agency: Air Resources Board, 2005), and the IARC (2004) publications have reviewed the evidence relating the risk of childhood brain tumors (CBTs) to SHS exposure. In addition to the studies presented in these reports, the effect of parental smoking on the risk of CBT was examined in a small hospital-based case-control study in China (Hu *et al*., 2000). Parents of 82 children with newly diagnosed primary malignant brain tumors were individually matched to 246 hospital controls from 1991 to 1996. There was little evidence to support an association between parents' smoking before or during pregnancy and risk of CBT. More recently, the association between CBTs (all histological types combined) and exposure of parents and children to cigarette smoke was evaluated in a comprehensive, large, international case-control study (Filippini *et al*., 2002).

Table 2.10a Exposure to SHS and stomach cancer - Cohort studies

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders
Hirayama, 1981 Japan 1966-1979	91 540 nonsmoking, married women ≥40 years (716 deaths due to stomach cancer)	Interviewer-administered questionnaire	Nonsmoking husband	1	Husband's age and occupation. Confidence intervals not provided
			Husband is ex-smoker or smokes 1-19 cig/day	1.02	
			Husband smokes ≥20 cig/day	0.99	
Hirayama, 1984 Japan 1966-1981	91 540 nonsmoking, married women ≥40 years (854 deaths due to stomach cancer)	Interviewer-administered questionnaire		**RR (90% CI)**	
			Nonsmoking husband	1	Husband's age
			Husband is ex-smoker	1.15 (0.93-1.43)	
			Husband smokes 1-14 cig/day	1.00 (0.86-1.17)	
			Husband smokes 15-19 cig/day	1.00 (0.81-1.22)	
			Husband smokes ≥20 cig/day	1.01 (0.86-1.19)	
			Nonsmoking husband	1	Husband's age and occupation
			Husband is ex-smoker or smokes 1-19 cig/day	1.03 (0.89-1.18)	
			Husband smokes ≥20 cig/day	1.05 (0.89-1.24)	

Table 2.10a Exposure to SHS and stomach cancer - Cohort studies

Reference, location, period	Cohort description	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders
Jee *et al.*, 1999 South Korea 1994-1997	157 436 nonsmoking, married women ≥40 years (197 stomach cancer cases)	Self-administered questionnaire	Husband never smoked	1	Age, husband's age, SES, residence, husband's vegetable consumption, husband's occupation
			Husband is ex-smoker	1.0 (0.7-1.5)	
			Husband is current smoker	0.9 (0.6-1.2)	
Nishino *et al.*, 2001 Japan 1984-1992	9675 nonsmoking women ≥40 years (83 stomach cancer cases)	Self-administered questionnaire	Nonsmoking husband	1	Age
			Husband smokes	0.95 (0.58-1.6)	
			Neither husband nor other household members smoke	1	
			Other household members smoke (and husband does not smoke)	0.90 (0.52-1.5)	
			Husband smokes (and other household members do not smoke)	0.91 (0.48-1.7)	
			Husband and other household members smoke	0.90 (0.45-1.8)	
			Nonsmoking husband	1	Age, study area, alcohol consumption, vegetable intake, fruit intake, miso soup intake, pickled vegetable intake
			Husband smokes	0.98 (0.59-1.6)	
			No other household member smoke	1	
			Other household members smoke	0.87 (0.54-1.4)	

Table 2.10b Exposure to SHS and stomach cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Sandler *et al.*, 1985a North Carolina, USA 1979-1981	518 cancer patients 15-59 years; 72% response rate	518 friend and community controls individually matched on gender, age and race; 75% response rate	Self-administered questionnaire	Nonsmoking spouse or never married Spouse smoked regularly (at least 1 cig/day for at least 6 months) any time during marriage	1 1.0 (0.5-2.2)	Age and education	Only 39 patients 15-59 years with cancer of the digestive system and 489 controls used
Sandler *et al.*, 1985b North Carolina, USA 1979-1981	470 cancer cases (any site); 70% overall response rate	438 controls, individually matched on gender, age and race	Self-administered questionnaire	Not exposed to SHS from mother during first 10 yrs of life SHS exposure from mother during first 10 yrs of life Not exposed to SHS from father during first 10 yrs of life SHS exposure from father during first 10 yrs of life	1 0.7 1 1.3	None	31 digestive cancer cases were used in the SHS analysis and all of the controls; results for nonsmokers presented; no CIs provided
Mao *et al.*, 2002 Canada 1994-1997	1171 cases of newly diagnosed, histologically confirmed cardial or distal stomach cancers; 63.2% overall response rate	207 population controls; 62.6% overall response rate	Self-administered questionnaire	**Cardial stomach cancer:** Never exposed to SHS at work or home 1-22 yrs SHS exposure at home or work 23-42 yrs SHS exposure at home or work 43+ yrs SHS exposure at home or work 1-55 smoker-yrs of SHS exposure at home or work	 1 3.5 (0.7-17.3) 2.8 (0.5-14.2) 5.8 (1.2-27.5) 2.5 (0.5-13.1)	Age, province, education, social class, meat, vegetable, fruit and juice consumption	Only never smoking men were used for the SHS exposure analysis

Table 2.10b Exposure to SHS and stomach cancer - Case-control studies

Reference, location, period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Mao *et al.*, 2002 Canada 1994-1997				56-125 smoker-yrs of SHS exposure at home or work	4.5 (0.9-21.8)		
				126+ smoker-yrs of SHS exposure at home or work	3.4 (0.7-17.0)		
				Distal stomach cancer: Never exposed to SHS at work or at home	1		
				1-22 yrs SHS exposure at home or work	0.5 (0.2-1.1)		
				23-42 yrs exposure at home or work	0.9 (0.5-1.7)		
				43+ yrs exposure at home or work	1.0 (0.5-2.0)		
				1-55 smoker-yrs of exposure at home or work	0.6 (0.3-1.3)		
				56-125 smoker-yrs of exposure at home or work	0.7 (0.3-1.4)		
				126+ smoker-yrs of exposure	1.1 (0.6-2.0)		

The study sample consisted of 1218 cases <20 years old and newly diagnosed with CBT and 2223 population-based controls. There was no association between the risk of CBT and mothers' smoking (OR=0.9; 95% CI=0.8-1.0) or paternal smoking (OR=1.1; 95% CI=0.9-1.2) prior to pregnancy, mother smoking during pregnancy (home or work) (OR=0.9; 95% CI=0.8-1.1), or SHS exposure of the child during the first year of life (OR=1.0; 95% CI=0.8-1.1). The findings did not change after adjusting for the child's age, histological type, or location. There was some variation across histological type. For example, risk of the primitive neuroectodermal tumors was significantly elevated in children who were regularly exposed during gestation through their mothers being involuntarily exposed to SHS at work (OR=1.3; 95% CI=1.0-1.8) or to all sources of SHS combined (OR=1.3; 95% CI=1.0-1.7). However, risk of other histological types was reduced in persons whose mother smoked until pregnancy (OR=0.7; 95% CI=0.5-1.0) and who were exposed during the first year of life (OR=0.7; 95% CI=0.5-1.0). However, these findings should be considered in the context of the large number of exposure groups and histological types and the related risk for type I error.

Is there a safe level of exposure to SHS?

Studies of the relation between level of exposure to SHS and risk of disease have not shown evidence of a level below which the excess risk is zero. That is, there are

no empirical data to support the concept of a safe (harm-free) level of exposure to SHS. This is not the same, of course, as demonstrating that there is no threshold (other than zero exposure). However, the epidemiological findings need to be considered alongside what is known about the toxicology of SHS and the likely biologic mechanisms of action, which are referred to earlier in this chapter. It was on this basis that the 2006 US Surgeon General's report concluded "the scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke" (U.S. Department of Health and Human Services, 2006). The Working Group agrees with this assessment.

Burden of disease

Because of widespread exposure to SHS and the numerous adverse consequences of exposure, the impact on the health of children and adults is substantial. The burden of disease attributable to SHS has been estimated for a number of populations. Making such estimations requires assumptions about exposure patterns and the risks of SHS-related diseases applicable to particular populations. While consequently subject to uncertainty, the available estimates document that SHS has substantial, while avoidable, public health impact. For example, estimates made by the State of California for both the state and for the entire USA (see Table ES-2 from the California EPA report), document thousands of premature deaths from cancer and ischemic heart disease, as well as over 400 deaths attributable to SIDS each year in the USA (Table 2.11). The morbidity burden for children is high (Table 2.11).

Estimates made for Europe with a similar approach led to the same conclusion on the public health significance of SHS exposure (Smoke Free Partnership, 2006). The report, *Lifting the Smokescreen: 10 Reasons for a Smokefree Europe,* provides estimates of the numbers of deaths attributable to SHS among nonsmokers in 25 European countries in 2002. The estimates are made with the assumptions of causal associations of SHS exposure with stroke and chronic respiratory disease, in addition to lung cancer and ischemic heart disease. The total burden is over 19 000 premature deaths annually.

Methods for estimating the burden of disease attributable to SHS (and other environmental exposures) at national and local levels have been reviewed recently by WHO (Prüss-Üstün & Corvalán, 2006). The burden of disease associated with SHS exposure varies from population-to-population with the profile of exposure and the underlying rates of disease. For adults, the burden of attributable disease is strongly dependent on the rate of coronary heart disease, which is a major contributor to mortality in many countries, not just in the wealthiest parts of the world.

Table 2.11 Contribution of SHS to the burden of disease in the United States - examples of health outcomes attributable to SHS

Outcome	Annual excess number due to SHS
Children born weighing <2500 g	24 500
Pre-term deliveries	71 900
Episodes of childhood asthma	202 300
Doctor visits for childhood otitis media	790 000
Deaths due to Sudden Infant Death Syndrome	430
Deaths due to Ischemic Heart Disease	46 000 (22 700 – 69 500)
Lung cancer deaths	3400

Adapted from California Environmental Protection Agency: Air Resources Board (2005)

Summary

This chapter describes the findings of review groups that have conducted comprehensive assessments of the health effects of exposure to SHS. Over the four decades that research findings on SHS and health have been reported, stronger conclusions of reviewing groups have progressively motivated the development of protective policies. The rationale for such policies is solidly grounded in the conclusions of a number of authoritative groups: that SHS exposure contributes to the causation of cancer, cardiovascular disease, and respiratory conditions.

The Working Group found a high degree of convergence of the research findings. In fact, since 1986, an increasing number of reports have added to an ever growing list of causal effects of SHS exposure. These reports have given exhaustive consideration to the epidemiological findings and the wide range of research supporting the plausibility of causal associations. They have also considered and rejected explanations other than causation for the associations observed in the epidemiological studies. Particular attention has been given to confounding by other risk factors and to exposure misclassification, both of active smoking status and of exposure to SHS.