

The most serious criticism is the misclassification of the active smoking status of the subjects, which can produce an apparent increased risk with involuntary smoking. Moreover, it is likely to result in differential misclassification because spouses tend to have similar smoking habits (Burch 1981; Sutton 1981; Higgins et al. 1967). Speculation that the positive results reported in Japan and Greece were due to cultural bias against the admission of smoking by women in these more traditional societies may be discounted because positive significant findings have now been observed in the United States (Correa et al. 1983; Garfinkel et al. 1985) and in Sweden (Pershagen et al., in press), where no comparable social stigma exists. Moreover, in the studies by Garfinkel and coworkers (1985) and Pershagen and coworkers (in press), the personal smoking status of each subject was validated and verified at interview, usually by next of kin, who presumably would have no reason to misrepresent the true smoking status of the subject.

Misclassification of the lung as the primary site and the lack of pathological confirmation are repeated concerns, but it must be stressed that this bias would tend to dilute a true effect. Correa (1983), Garfinkel (1985), and Pershagen (in press) and their respective colleagues addressed this issue by including only pathologically confirmed lung cancers and considering histological cell type in their analyses. In the study by Garfinkel and associates (1985), after an independent pathological review was conducted, a significant association of excess risk with involuntary smoking remained. Misclassification of exposure to ETS cannot be dismissed, since an index based solely on the smoking habits of a current spouse may not be indicative of past exposure, cumulative exposure, or the relevant dose to the respiratory tract.

The magnitude of risk associated with involuntary smoking exposure is uncertain. Relative risks ranging from 2 to 3 were generally reported for the highest level of exposure based on the spouses' smoking habits, but since sample sizes in most studies are not large, the point estimates of effect are unstable, and confidence limits are broad and generally overlap from one study to another. An index of involuntary smoking based on the smoking habits of the spouse is a simplistic and convenient measure. There is no reason to believe, however, that the excess risk associated with involuntary smoking is restricted to exposure from spouses. Nonsmokers married to smokers are likely to be more tolerant of ETS exposure and to experience more exposure to environmental tobacco smoke (Wald and Ritchie 1984). Higher risk estimates for involuntary smoking have been obtained in studies restricted to squamous cell and small cell carcinomas of the lung.

Although involuntary smoking can be established as a cause of lung cancer, important questions related to this exposure require

further research. More accurate estimates for the assessment of exposure in the home, workplace, and other environments are needed. Studies of sufficiently large populations should also be performed. New data from such studies should yield more certain risk estimates and describe the magnitude of the lung cancer risk in nonsmokers.

Other Cancers

Several recent studies provide data on the relationship of ETS exposure to cancer at sites other than the lung. Two published reports address the risk of other cancers in adults from exposure to tobacco smoke from spouses. Using the same Japanese cohort described previously, Hirayama (1984a) reported excess mortality for cancers of the paranasal sinus (N=28) and brain (N=34) among nonsmoking women who were married to smokers. The standardized mortality ratios (SMRs) for nasal sinus cancer were 1.00, 1.67, 2.02, and 2.55 for women whose husbands never smoked, or had smoked 10 to 14, 15 to 19, or 20 or more cigarettes per day, respectively (one-sided p for trend, 0.03). The corresponding SMRs for brain tumors were 1.00, 3.03, 6.25, and 4.32, respectively (one-sided p for trend, 0.004). The total number of deaths due to nasal cancer and brain tumors was small, and the numerators in the risk calculations were unstable, based on five nasal cancers and three brain cancers in women whose husbands were nonsmokers. In one study (Brinton et al. 1984), active tobacco smoking was associated with an increased risk of sinus cancer, particularly squamous cell tumors. Sidestream smoke has also been suggested to be of etiological importance in brain tumors in children (Preston-Martin et al. 1982).

In a case-control study of adult cancers in relation to childhood and adult exposure to involuntary smoking, Sandler and coworkers (1985a, 1986) reported an overall cancer risk of 1.6 (95 percent C.I. 1.2, 2.1) associated with exposure to spouses' smoking, which was more marked in nonsmokers than smokers. Significant increases were observed for cancer of the breast (OR 1.8), cervix (OR 1.8), and endocrine organs (OR 3.2). This study has been criticized in its choice of controls and in the exclusion of certain cancers by the design of the study. The biological plausibility of the study's findings was also questioned because the highest risk estimates were observed for cancers that have not been consistently related to active smoking and because higher risks were observed for nonsmokers than for smokers. Failure to control for potential confounding factors and known risk factors for the individual cancer sites under study may have produced artifactual results (Friedman 1986; Mantel 1986; Burch 1986). In a subsequent analysis of the same study population, Sandler, Wilcox, and Everson (1985a,b) reported increasing cancer

risks with increasing exposure to involuntary smoking as measured by the number of smokers in the household and by the time periods of exposure. The biologic plausibility of these findings was also questioned (Burch 1985; Higgins 1985; Lee 1985).

The effect of parental smoking on the development of cancers both during childhood and in adult life is also of interest. The relationship of parental smoking to overall cancer risk in children or in adults has been assessed in three studies. A prospective survey (Neutel and Buck 1971) of about 90,000 infants in Canada and the United Kingdom followed for a maximum of 10 years found an overall cancer risk of 1.3 (95 percent C.I. 0.8, 2.2) associated with maternal smoking during pregnancy. No dose-response relationship was observed, but there were few heavy smokers (>1 pack/day) in this study. A Swedish case-control study (Stjernfeldt et al. 1986) of all cancers found a risk of 1.4 (95 percent C.I. 1.0, 1.9) for maternal smoking during pregnancy. A dose-response relationship was demonstrated; the risk was highest in the most exposed group, those smoking 10 or more cigarettes per day (RR 1.6, $p < 0.01$). On the basis of the smoking habits of the parents of subjects up to 10 years of age, Sandler, Everson, Wilcox, and Browder (1985) reported no significant difference between all cancer cases and controls with respect to the mother's smoking (RR 1.1, 95 percent C.I. 0.7, 1.6), but the father's smoking was related to an overall increased risk (RR 1.5, 95 percent C.I. 1.1, 2.0). In these three studies, analysis by specific cancer site revealed an increased risk of leukemia associated with parental smoking.

Neutel and Buck (1971) found an almost twofold increased risk of leukemia in children of mothers who smoked during pregnancy, but the association was not statistically significant. Stjernfeldt and colleagues (1986) reported a significant positive association between maternal smoking and acute lymphoblastic leukemia. The relative risks were 1.0, 1.3, and 2.1 (p for trend, < 0.01) for mothers who smoked 0, 1 to 9, and 10 or more cigarettes per day, respectively. Similar significant positive associations with maternal smoking were not observed for other cancer sites, but the risk assessments were based on a small number of cases. This study suggests that the relationship between maternal smoking and leukemia was strongest for smoking during the 5-year period before pregnancy, intermediate for smoking during pregnancy, and lowest for smoking after pregnancy. In the study by Sandler, Everson, Wilcox, and Browder (1985), the mother's smoking and the father's smoking were separately and jointly associated with an increased risk for leukemia and lymphoma. The relative risk was 1.7 when one parent smoked and 4.6 when both parents smoked (p for trend, < 0.001). The increased risk with parental smoking was observed regardless of the personal smoking status of the subject. No other cancer site was associated

with the mother's smoking, although the father's smoking was associated with increased risks for other cancer sites, including the brain and the cervix. Two studies of leukemia in children found no relationship with parental smoking (Manning and Carroll 1957; Van Steensel-Moll et al. 1985). In the study by Manning and Carroll (1957), the mothers' general smoking habits were assessed, whereas Van Steensel-Moll and colleagues (1985) obtained information on the smoking habits of both parents in the year before the pregnancy. Stewart and colleagues (1958) reported a statistically significant risk of 1.1 ($p=0.04$) for leukemia in association with the mothers' smoking, but cautioned that the smoking information on the mothers pertained to their habits at the time of interview, which took place after the deaths of the patients and may have been affected by bereavement.

The effect of parental smoking habits has been examined in epidemiological studies of brain tumors, rhabdomyosarcoma, and testicular cancer in children. Gold and colleagues (1979) reported an association between maternal smoking prior to and during pregnancy and brain tumors in children. A relative risk of 5.0 ($p=0.22$) was found, but the result was based on a small number of patients and was not statistically significant. No relationship between maternal smoking during pregnancy (RR 1.1, one-sided $p=0.42$) and brain tumors in children was found in another study (Preston-Martin et al. 1982), but a significantly increased risk (RR 1.5, one-sided $p=0.03$) associated with mothers living with a smoker (usually the child's father) during pregnancy was observed. A significantly increased risk with the father's smoking, but not the mother's smoking was also reported in a study of rhabdomyosarcoma (Grufferman et al. 1982). The father's smoking conferred a significant increase in risk (RR 3.9, 95 percent C.I. 1.3, 9.6), but the mother's smoking during and after the pregnancy was not significantly different between cases and controls (RR 0.8, 95 percent C.I. 0.3, 2.0). A history of maternal smoking during pregnancy did not differ for testicular cancer cases and controls (RR 1.0, $p=0.57$) in one study (Henderson et al. 1979).

There are at present insufficient data to adequately evaluate the role of involuntary smoking in adult cancers other than primary carcinoma of the lung. In addition, active smokers necessarily receive greater exposure to ETS than nonsmokers. Thus, effects would not be anticipated in involuntary smokers that do not occur in active smokers (IARC 1986), and the biological plausibility of associations between ETS exposure and cancer of sites not associated with active smoking must be questioned. The findings of Hirayama (1984a) and Sandler, Everson, and Wilcox (1985) need confirmation in studies that take into account the potential confounding factors and the known risk factors for these individual sites. The evidence

for parental smoking and childhood cancer is also not clear, and evaluation of this association is made difficult by the various definitions of exposure that have been used, including maternal and paternal smoking before, during, and after the pregnancy. Mothers and fathers who smoke during a pregnancy generally smoked before the conception and continue to smoke after the pregnancy. Thus, an effect of involuntary smoking after birth cannot readily be distinguished from genetic or transplacentally mediated effects.

Cardiovascular Diseases

A causal association between active cigarette smoking and cardiovascular disease is well established (US DHHS 1983). The relationship between cardiovascular disease and involuntary smoking has been examined in one case-control study and three prospective studies. In the case-control study by Lee and colleagues (1986), described previously, ischemic heart disease cases and controls did not show a statistically significant difference in their exposure to involuntary smoking, based on the smoking habits of spouses or on an index accounting for exposure at home, at work, and during travel and leisure. In the Japanese cohort study, Hirayama (1984b, 1985) reported an elevated risk for ischemic heart disease (N=494) in nonsmoking women married to smokers. The standardized mortality ratios when the husbands were nonsmokers, ex-smokers or smokers of 19 or more cigarettes per day, and smokers of 20 or more cigarettes per day were 1.0, 1.10, and 1.31, respectively (one-sided p for trend, 0.019).

In the Scottish followup study (Gillis et al. 1984), nonsmokers not exposed to tobacco smoke were compared with nonsmokers exposed to tobacco smoke with respect to the prevalence of cardiovascular symptoms at entry and mortality due to coronary heart disease. There was no consistent pattern of differences in coronary heart disease or symptoms between nonsmoking men exposed to tobacco smoke and their nonexposed counterparts. Nonsmoking women exposed to tobacco smoke exhibited a higher prevalence of angina and major ECG abnormality at entry, and also a higher mortality rate for all coronary diseases. However, rates of myocardial infarction mortality were higher for exposed nonsmoking men and women compared with the nonexposed nonsmokers. The rates were 31 and 4 per 10,000, respectively, for the nonexposed nonsmoking men and women, and 45 and 12 per 10,000, respectively, for the exposed nonsmoking men and women. None of the differences were tested for statistical significance.

In the Japanese and the Scottish studies, other known risk factors for cardiovascular diseases, i.e., systolic blood pressure, plasma cholesterol, were not accounted for in the analysis.

In a study of heart disease, Garland and coworkers (1985) enrolled 82 percent of adults aged 50 to 79 between 1972 and 1974 in a predominantly white, upper-middle-class community in San Diego, California. Blood pressure and plasma cholesterol were measured at entry, and all participants responded to a standard interview that asked about smoking habits, history of heart disease, and other health-related variables. Excluding women who had a previous history of heart disease or stroke or who had ever smoked, 695 currently married nonsmoking women were classified by their husbands' self-reported smoking status at enrollment. After 10 years of followup, there were 19 deaths due to ischemic heart disease; the age-standardized mortality rates for nonsmoking wives whose husbands were nonsmokers, ex-smokers, and current smokers were 1.2, 3.6, and 2.7, respectively (one-sided p for trend, ≤ 0.10). After adjustment for age, systolic blood pressure, total plasma cholesterol, obesity index, and years of marriage, the relative risk for death due to ischemic heart disease for women married to current or former smokers at entry compared with women married to never smokers was 2.7 (one-sided $p \leq 0.10$).

The study's findings are not convincing from the point of view of sample stability. The total number of deaths due to ischemic heart disease was small, and the denominator in the relative risk calculation is unstable, based on the deaths of two women whose husbands had never smoked. Moreover, it is well established that the risk of coronary heart disease is substantially lower among those who have stopped smoking (US DHHS 1983), although the amount of time required for this change after cessation of smoking is not clear (Kannel 1981). In this study, 15 of 19 deaths occurred in nonsmoking women married to husbands who had stopped smoking at entry, and the age-standardized rate for ischemic heart disease was highest in this group. The high proportion of deaths in nonsmoking women married to men who became ex-smokers implies that the excess resulted from a sustained effect of involuntary smoking. More detailed characterizations of exposure to ETS and specific types of cardiovascular disease associated with this exposure are needed before an effect of involuntary smoking on the etiology of cardiovascular disease can be established.

One study (Aronow 1978a,b) suggested that involuntary smoking aggravates angina pectoris. This study was criticized because the end point, angina, was based on subjective evaluation, and because other factors such as stress were not controlled for (Coodley 1978; Robinson 1978; Waite 1978; Wakehan 1978). More important, the validity of Aronow's work has been questioned (Budiansky 1983).

Conclusions

1. Involuntary smoking can cause lung cancer in nonsmokers.
2. Although a substantial number of the lung cancers that occur in nonsmokers can be attributed to involuntary smoking, more data on the dose and distribution of ETS exposure in the population are needed in order to accurately estimate the magnitude of risk in the U.S. population.
3. The children of parents who smoke have an increased frequency of hospitalization for bronchitis and pneumonia during the first year of life when compared with the children of nonsmokers.
4. The children of parents who smoke have an increased frequency of a variety of acute respiratory illnesses and infections, including chest illnesses before 2 years of age and physician-diagnosed bronchitis, tracheitis, and laryngitis, when compared with the children of nonsmokers.
5. Chronic cough and phlegm are more frequent in children whose parents smoke compared with children of nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study.
6. The children of parents who smoke have small differences in tests of pulmonary function when compared with the children of nonsmokers. Although this decrement is insufficient to cause symptoms, the possibility that it may increase susceptibility to chronic obstructive pulmonary disease with exposure to other agents in adult life, e.g., active smoking or occupational exposures, needs investigation.
7. Healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone.
8. A number of studies report that chronic middle ear effusions are more common in young children whose parents smoke than in children of nonsmoking parents.
9. Validated questionnaires are needed for the assessment of recent and remote exposure to environmental tobacco smoke in the home, workplace, and other environments.
10. The associations between cancers, other than cancer of the lung, and involuntary smoking require further investigation before a determination can be made about the relationship of involuntary smoking to these cancers.
11. Further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to

determine whether involuntary smoking increases the risk of cardiovascular disease.

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CHAPTER 3

ENVIRONMENTAL TOBACCO SMOKE CHEMISTRY AND EXPOSURE OF NONSMOKERS

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Introduction

The physicochemical nature of environmental tobacco smoke (ETS) is governed by the type and form of the tobacco product or products burned, by the prevailing environmental conditions, and by secondary reactions. Mainstream smoke (MS) is the complex mixture that exits from the mouthpiece of a burning cigarette, cigar, or pipe when a puff is inhaled by the smoker. Sidestream smoke (SS) is formed between puff-drawings and is freely emitted into the air surrounding a smoldering tobacco product. Sidestream smoke represents the major source for ETS. The exhaled portions of MS and the vapor phase components that diffuse through the wrapper into the surrounding air constitute minor contributors to ETS.

In the scientific literature, the terms "passive smoking," "involuntary smoking," and "inhalation of ETS" are frequently used interchangeably (US DHEW 1979; US DHHS 1982, 1984).

Laboratory Smoking

Data on the composition of MS and SS originate from laboratory studies. For such studies, cigarettes, cigars, or pipes are smoked by machines under standardized reproducible conditions. It is a major goal of these measurements to compare the yields of the specific components in the MS or SS or both of a variety of experimental or commercial tobacco products and to simulate, though not to reproduce, human smoking habits. The most widely used standard conditions for machine smoking cigarettes and little cigars (≤ 1.5 g) are one 35 mL puff of 2-second duration drawn once a minute to a butt length of 23 mm, or the length of the filter tip plus the overwrap plus 3 mm (Brunnemann et al. 1976). The annual reports of the U.S. Federal Trade Commission on the tar, nicotine, and carbon monoxide content of the smoke of U.S. commercial cigarettes are based on these laboratory smoking conditions. For cigars, the standard smoking conditions are a 20 mL puff of 1.5-second duration taken once every 40 seconds, and a butt length of 33 mm (International Committee for Cigar Smoke Study 1974). The most frequently used pipe-smoking conditions call for the bowl to be filled with 1 g of tobacco and a 50 mL puff of 1-second duration to be taken every 12 seconds (Miller 1964).

A number of devices for collecting sidestream smoke have been developed (Dube and Green 1982). The most widely used device is a collection apparatus made of glass and cooled by water circulating through an outer jacket. The air entering the chamber through a distributor has a flow rate of 25 mL per second (1.5 L/min) (Brunnemann and Hoffmann 1974). Under these conditions, the yields of mainstream smoke components from a cigarette approximate those obtained from the same cigarette when it is being smoked