sources) (Sterling 1981). However, Hirayama showed a fairly consistent relationship between involuntary smoking exposure and lung cancer across SES categories. The role of indoor air pollutants could not be addressed directly in the study, but data from one health district in the study indicated no association between heating or cooking practices and the smoking habits of the husbands (Hirayama 1981b).

The researcher's failure to specifically describe the methods for age standardization in the initial report led to speculation that the statistical methods used were incorrect (Kornegay and Kastenbaum 1981; Mantel 1981; Tsokos 1981; Lee 1981); however, the calculations were later confirmed (Harris and DuMouchel 1981; Hammond and Selikoff 1981). The choice of stratification variables used for age standardization was also criticized because the husbands' ages instead of the wives' ages and 10-year age groups instead of narrower ones were used (Tsokos 1981; MacDonald 1981b). Later publications confirmed that similar results were obtained regardless of the method of standardization (Hirayama 1984a).

The American Cancer Society Cohort Study

A second prospective study (Garfinkel 1981) that examined the effects of involuntary smoking was the American Cancer Society (ACS) study of about 1 million people living in 25 States. A self-administered questionnaire on education, residence, occupational exposure, and smoking and medical history was completed by the study subjects upon enrollment.

This report on involuntary smoking was based on 12 years of followup (1960–1972) and included 176,739 nonsmoking married women whose husbands' smoking habits were available and whose husbands were never smokers or current smokers. In the total cohort of nonsmoking women, 564 lung cancer deaths occurred, and data on the husbands' smoking habits were available for 153 (27.1 percent). Wives of ex-smokers and of cigar or pipe smokers were excluded from the analysis.

A small, statistically nonsignificant increased risk for lung cancer was found for nonsmokers married to smokers. The mortality ratios for lung cancer in nonsmoking women were 1.0, 1.27, and 1.10 when the husbands were nonsmokers, daily smokers of fewer than 20 cigarettes, and daily smokers of 20 or more cigarettes, respectively. The results were essentially unchanged after accounting for the potential confounding effects of age, race, education, residence, and husband's occupational exposure.

The ACS study, like the Japanese study, was not designed to study the long-term effects of involuntary smoking. However, the ACS study does provide an estimate of the extent of misclassification of lung cancer. On the basis of medical record verification, the death

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certificate diagnosis of lung cancer in nonsmoking women was incorrect for 12 percent of the cases. Although confirmation of diagnosis was sought only for the first 6 years of followup, the available data suggest that some misclassification of lung cancer occurred. To the extent that passive smoking is related to lung cancer in nonsmokers, inclusion of nonlung cancers would tend to dilute a true effect.

A limitation of the ACS study is the nonavailability of smoking information on the husbands of a large proportion of the nonsmoking women who died of lung cancer. Because smoking habits are correlated with various social characteristics, this large loss of information may have created a bias in this study. The researcher stated that an index of tobacco smoke exposure based only on smoking habits of current husbands may be particularly inadequate for the United States, with its high rate of divorce and substantial proportion of women working outside the home. This speculation is supported by data from a group of 37,881 nonsmokers and ex-smokers who were members of a health plan in California. Friedman and colleagues (1983) stated that 47 percent of the nonsmoking women and 39 percent of the nonsmoking men married to smokers reported no exposure at home. Moreover, being married to a nonsmoker did not assure the absence of exposure to tobacco smoke, since 40 percent of the nonsmoking women and 49 percent of the nonsmoking men married to nonsmokers reported some exposure to tobacco smoke during the week. Thus, random misclassification could have biased the results toward unity and led to an underestimate of the effect of passive smoking.

The Scottish Study

Gillis and colleagues (1984) conducted a prospective cohort study of 16,171 Scottish men and women, aged 45 to 64 years, from two urban areas, who attended a multiphasic health screening clinic between 1972 and 1976. A questionnaire on smoking habits and symptoms of respiratory and cardiovascular diseases was completed at entry into the study.

The preliminary analysis of involuntary smoking, representing 6 to 10 years of followup, was based on the 2,744 nonsmokers among the 8,128 subjects who lived as couples and could be paired according to smoking habits. Subjects who lived alone or whose partner did not participate and ex-smokers who had stopped smoking for 5 years or more were excluded. The nonsmokers were classified as nonsmokers not exposed to environmental tobacco smoke or as nonsmokers exposed to environmental tobacco smoke, according to the smoking habits of their spouses.

A higher age-standardized lung cancer mortality rate was reported for nonsmoking men exposed to tobacco smoke (13 per 10,000) than

for nonsmoking men not exposed (4 per 10,000); however, no statistical tests were conducted because of the small number of cancers. Lung cancer rates were similar for nonsmoking women regardless of the status of their exposure to tobacco smoke (4 per 10,000). The extremely small number of observed lung cancer deaths (6 men, 8 women) limit the interpretation of the study's findings.

Spousal Exposure: Case-Control Studies

Table 8 summarizes the case-control studies that have examined the relationship between involuntary smoking exposure and lung cancer.

The Greek Study

Trichopoulos and colleagues (1981, 1983; Trichopoulos 1984) examined the effect of involuntary smoking on lung cancer risk in a case-control study of 51 Caucasian female lung cancer patients (excluding adenocarcinoma and terminal bronchiolar carcinomas) from three chest hospitals and 163 female controls from an orthopedic hospital in Athens, Greece. All subjects were interviewed in person by one physician who questioned them regarding their personal smoking habits and those of their current and former husbands. Thirty-five percent of the cases were diagnosed only on the basis of clinical or radiologic information; the remainder were cytologically (37 percent) or histologically (28 percent) confirmed.

Nonsmoking women were classified by the smoking habits of their current or former husbands. Husbands were nonsmokers if they had never smoked or had stopped smoking more than 20 years previously, ex-smokers if they stopped 5 to 20 years previously, and current smokers if they were smoking or had stopped less than 5 years before the interview. Being never married, widowed, or divorced was equated as being married to a nonsmoker or an ex-smoker, depending on the length of time in the category.

The initial report was based on 40 nonsmoking cases and 149 nonsmoking controls. The odds ratios (ORs) for women married to nonsmokers, ex-smokers, current smokers of 1 to 20 cigarettes per day, and current smokers of 21 or more cigarettes per day were 1.0, 1.9, 2.4, and 3.4, respectively (two-sided p for trend, <0.02). In a later report on 77 nonsmoking cases and 225 nonsmoking controls, the ORs were somewhat lower: 1.0, 1.9, 1.9, and 2.5, respectively (Trichopoulos et al. 1983; Trichopoulos 1984).

The findings of this study were questioned because the diagnosis of cancer was not pathologically confirmed for 35 percent of the cases (Hammond and Selikoff 1981; Lee 1982b). The inclusion of cases that were not lung cancers would tend to dilute the results toward the null because they may not be related to involuntary smoking.

Terminal bronchial (alveolar) carcinoma and adenocarcinoma of the lung were excluded from the pathologically confirmed group; this exclusion may have been premature (Hammond and Selikoff 1981; Kabat and Wynder 1984), as the causal association between personal smoking and adenocarcinoma of the lung is well established (IARC 1986). Because the controls were selected from a different hospital than were the cases, selection bias cannot be ruled out. Interviewer bias is also possible, since all subjects were interviewed by a single physician who knew the case or control status of each subject, and also knew the hypothesis under investigation.

The index of exposure to tobacco smoke used in this study included the smoking habits of former and current husbands. Since the definition of ex-smokers excluded those who had stopped smoking recently (within the last 5 years), it was unanticipated that the risks observed for women whose husbands were ex-smokers (i.e., quit 5 to 20 years previously) were as high as for those whose husbands were current smokers. Additional information on the smoking habits of these ex-smokers would be valuable.

The Louisiana Study

The case–control study by Correa and colleagues (1983) was based on 1,338 primary lung cancer cases, of which 97 percent were pathologically confirmed. Controls (N=1,393) were matched to cases by race, sex, and age (±5 years) and were patients at the same hospitals as cases but without a diagnosis related to tobacco smoking.

Standardized interviews were conducted with the subjects (76 percent of cases, 89 percent of controls) or their next of kin. Questions on occupation, residency, personal smoking and drinking habits, and smoking habits (including type of tobacco smoked and amount and duration of smoking) of the current spouse and parents were asked.

Thirty nonsmoking ever-married lung cancer (excluding bronchioalveolar cell) patients (8 men, 22 women) and 313 ever-married nonsmoking controls (180 men, 133 women) were classified according to their spouse's total lifetime pack-years and current daily amount smoked at the time of interview. After adjusting for sex, ORs of 1.00, 1.48, and 3.11 were observed when spouses had smoked none, 1 to 40 pack-years, and 41 or more pack-years, respectively (two-sided $p < 0.05$). The results based on current daily number of cigarettes smoked by spouses were similar.

The study is limited by the small number of nonsmoking cases, but the consistency of the results for men and women strengthens the findings. Misclassification of involuntary smoking is possible because only smoking habits of the current husband were assessed, ignoring the effect of divorce, remarriage, and exposure from coworkers. Exposure from parents during childhood was determined, but case

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numbers were too small for a meaningful analysis of this factor among nonsmokers.

The Hong Kong Studies

The high rates of lung cancer, particularly adenocarcinoma of the lung, among women of Chinese descent in Hong Kong are unexpected in the face of their low rates of tobacco smoking. The role of involuntary smoking was investigated in two studies conducted in Hong Kong (Chan et al. 1979; Chan and Fung 1982; Koo et al. 1983, 1984).

Chan and colleagues (1979) examined the role of involuntary smoking among 84 female lung cancer patients and 139 orthopedic control patients, none of whom had ever smoked. Of the 84 nonsmoking cases, 69 (82 percent) were pathologically confirmed, and 38 of these 69 cases were adenocarcinoma of the lung. The controls were from the same hospitals as the cases, but were not individually matched to the cases on any characteristics.

Cases and controls were questioned regarding their residence, education, occupation, cooking practices, and personal smoking habit. One question on exposure to others' tobacco smoke was included: "Are you exposed to the tobacco smoke of others at home or at work?" The researchers reported that the controls lived with smoking husbands more frequently (47.5 percent) than the cases (40.5 percent) (OR 0.77), but did not explain how this question was used to classify the habits of the spouse alone. The method used to classify currently unmarried respondents (i.e., never married, widowed, divorced) with regard to exposure to their spouses' smoking was not described, and it is not known if the nonsmoking cases and controls were comparable in terms of current marital and employ-- ment status. Thus, insufficient information on the measure used to assess ETS exposure, and on the comparability of the nonsmoking cases and controls, limits interpretation of this study's results.

The study by Koo and colleagues (1983, 1984) involved 200 Chinese female lung cancer patients who were identified from eight hospitals in Hong Kong; almost all cases were pathologically confirmed (97 percent). Among these women, 88 had never smoked, of whom 52 (59 percent) had adenocarcinomas of the lung. An equal number of "healthy" population controls, individually matched to cases by age (±5 years), socioeconomic status, and district of residence, were interviewed. Among the controls, 137 had never smoked.

Using a semistructured questionnaire, taped interviews were obtained and information on residence, occupation, family and medical history, personal smoking habits, and smoking habits of all cohabitants and coworkers was elicited. ETS exposure was quantified in hours and years according to who (i.e., husband, parents, in-laws, children, others) smoked in the subject's presence and where

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(i.e., at home, at work) the exposure occurred. The analysis was based on a cumulative smoke exposure index (in total hours and total years) specific to place of exposure.

The investigators concluded that there was no association between involuntary smoking and lung cancer in nonsmoking Chinese women, regardless of the index of smoke exposure used. A small, but statistically nonsignificant, increased risk (RR 1.24) was associated with any exposure to tobacco smoke. There were no significant differences between the cases and the controls in total hours or total years of exposure. The results remained unchanged when exposure hours were categorized into three levels of exposure. Odds ratios of 1.00, 1.28, and 1.02 were associated with no, low ($\leq$ 35,000 hours), and high (> 35,000 hours) exposure levels, respectively. There was no apparent trend of lung cancer risk with the age when exposure to tobacco smoke began. The ORs for never exposed and first exposed at ages 0 to 19, 20 to 39, and 40 or older were 1.00, 0.96, 1.53, and 0.91, respectively (Koo et al. 1984). Analysis by cell type suggested that the effects of involuntary smoking may be more pronounced for Kreyberg I tumors (squamous, small-cell, and large-cell carcinomas) (OR 1.47, 95 percent C.I. 0.64, 3.36) than for adenocarcinoma (OR 1.11, 95 percent C.I. 0.49, 2.50) (Koo et al. 1985), but these numbers were small.

The design of this study addressed the criticisms of other studies that an index of involuntary smoking exposure based only on spouses' smoking habits is inadequate, and broadened the exposure assessment to include all locations of tobacco smoke exposure. However, the cumulative exposure index created in this study may have limited validity. Unlike personal smoking, where there is essentially one source (personal smoking), one dose (usual or maximum amount smoked), and one duration of exposure (age at start and age at stop), ETS exposure derives from diverse sources at different doses and durations of exposure. The accuracy of the information on exposure to ETS will depend on the amount of detail requested, the age of the respondent, the temporal course of the exposure, and the source of the exposure. Weighing each type of exposure equally in a cumulative index (in total hours) may be incorrect because it assumes that all sources of exposure should be quantified in the same way and that each source of tobacco smoke contributes equally, disregarding intimacy of contact and proximity to smokers and conditions of exposure (e.g., room size, ventilatory factors). Thus, random misclassification of the exposure variable by inclusion of data from less relevant exposures than spousal smoking may obscure an association of involuntary smoking exposure with lung cancer risk. In this study, interviewer and respondent bias should also be considered because a structured questionnaire was not used.

An Ongoing Study of Tobacco-Related Cancers

All of the cases of primary lung cancer in nonsmokers were selected (Kabat and Wynder 1984) from an ongoing case–control study of tobacco-related cancer conducted in five U.S. cities between 1971 and 1980 (Wynder and Stellman 1977). For each case, one control was individually matched by age (± 5 years), sex, race, hospital, date of interview (± 2 years), and nonsmoking status. Controls were selected from a large pool of hospitalized patients who were interviewed over the same time period as the cases and who had diseases not related to tobacco smoking. Information on demographic factors, residence, height and weight, drinking habits, previous diseases, and occupational exposure were obtained. Questions on tobacco smoke exposure at work, at home, and from current spouse were added in 1978 and revised in 1979. Information on ETS exposure was available for 25 of 37 nonsmoking male cases, 53 of 97 nonsmoking female cases, and their respective matched controls.

A higher percentage of female controls than of female cases reported exposure to ETS at home (32 percent), at work (59 percent), and from spouses (60 percent). The percentages of female cases who reported exposure at home, at work, and from spouses were 30, 49, and 54 percent, respectively. None of the case–control differences in women were statistically significant. Male cases reported more frequent exposure at work (OR 3.27, p=0.045) and at home (OR 1.26), but no difference in the smoking status of their spouses (OR 1.00).

The process for selecting the nonsmoking controls from the larger pool of controls in the ongoing study and for selecting the non-smoking cases and controls who were questioned with regard to ETS exposure was not described adequately. It is not clear whether the 25 of 37 male and 53 of 97 female nonsmoking cases and controls who provided information on involuntary smoking were all interviewed during or after 1978 when the questions on involuntary smoking were introduced. The proportion seemed high, since it represented 68 percent of male and 55 percent of female nonsmoking cases interviewed during the 10 years of data collection. The study was not designed to specifically address the effect of involuntary smoking, and a variable subset of questions on involuntary smoking was asked, depending on when the subjects were interviewed. Misclassification of the exposure is possible because it is not clear whether the cases and controls answered the same set of questions and whether a comparable amount of information was obtained. The researchers acknowledged the limitations of this study and presented its results as preliminary findings.

The Los Angeles County Study

In the case–control study by Wu and colleagues (1985), 220 white female lung cancer patients (149 with adenocarcinoma and 71 with squamous cell carcinoma) and 220 population controls were individually matched on sex, race, age (±5 years), and neighborhood of residence. Cases were identified from the population-based tumor registry of Los Angeles County. All cases were histologically confirmed; the histological type was based on the pathology report from the hospital of diagnosis.

Using a structured questionnaire, cases and controls were directly interviewed by telephone and were asked about their own personal smoking habits and the smoking habits (amount and years of smoking) of current and former husbands, parents, and other household members during childhood and adult life. Exposure to tobacco smoke at work (in hours per day) was obtained for each job of at least 6 months' duration. Information on medical and reproductive history, heating and cooking sources, and dietary intake of vitamin A were obtained.

Of 149 patients with adenocarcinoma of the lung, 29 had never smoked, nor had 2 of 71 patients with squamous cell carcinoma. The analysis of involuntary smoking was based on the 29 nonsmokers among the adenocarcinoma cases and 62 nonsmokers among the controls.

A subject was classified as married to a smoker if any of her husbands had ever smoked. Similarly, a subject was considered exposed at work if she was exposed to tobacco smoke for at least 1 hour per day at any of her jobs. There were small, but nonsignificantly increased risks associated with ETS exposure from spouse or spouses (OR 1.2; 95 percent C.I. 0.2, 1.7), and from coworkers (OR 1.3; 95 percent C.I. 0.5, 3.3). Increased risk was not associated with smoke exposure from either parent (OR 0.6; 95 percent C.I. 0.2, 1.7). Exposure to tobacco smoke from spouses and from coworkers was combined in an index representing smoke exposure during adult life. There was an increasing trend in risk with increasing years of exposure. The ORs were 1.0, 1.2, and 2.0 for 0, 1 to 30, and 31 or more years of involuntary smoking exposure during adult life, respectively, but the results were not statistically significant. Because the exposures may have occurred concurrently, the years of exposure represented units of exposure rather than calendar years of exposure.

This study is limited by the small number of nonsmoking cases and controls. Unlike the two case–control studies that excluded adenocarcinoma or bronchioalveolar cell carcinoma (Trichopoulos et al. 1981; Correa et al. 1983), cases in this analysis were of these cell types (17 adenocarcinoma, 12 bronchioalveolar); this case mix may explain the weak association observed.

The Four Hospitals Study

A case–control study by Garfinkel and colleagues (1985) included 134 nonsmoking female lung cancer cases selected from three hospitals in New Jersey and one in Ohio over an 11-year period, 1971–1981. Medical records served as the initial source of information on smoking status of the subject, and the nonsmoking status of each case and control was verified at interview. Three controls, colorectal cancer patients matched to cases by age (±5 years) and hospital, were interviewed for each case, giving a total of 402 controls. All diagnoses of cases and controls were pathologically confirmed. Interviewers, blinded to the diagnosis of the subjects and to the study hypothesis, administered a standard questionnaire to subjects or their next of kin. Information on the smoking habits of current spouse (total and amount smoked at home), tobacco smoke from other sources (in hours per day at home, at work, and in other settings), and exposure to tobacco smoke during childhood were obtained.

Subjects were classified according to the smoking habits of current husbands. Smoking habits of a cohabitant in the same household was used for single women or those who no longer lived with their spouses. Of the cases, 57 percent were classified according to the smoking habits of husbands; the corresponding percentage in controls was not provided. Nonsmoking women living with a smoker showed an elevated risk for lung cancer (OR 1.31). The ORs for lung cancer in nonsmoking women were 1.00, 1.15, 1.08, and 2.11 when the husbands were nonsmokers, daily smokers of less than 10, 10 to 19, and 20 or more cigarettes at home, respectively (one-sided p for trend, < 0.025). Similarly, a significant positive linear trend (one-sided $p < 0.025$) was shown when the husbands' total amount smoked was categorized into four levels. However, there was no apparent dose-related trend by years of exposure to the husbands' smoking (0, $< 20, 20–29, 30–39, 40+$ years).

There was no apparent association between lung cancer and tobacco smoke exposure from other sources. Cases and controls did not differ in their reported exposure to tobacco smoke during childhood or in their average hours of exposure per day to other's tobacco smoke during the last 5 years and 25 years before diagnosis. The results remained unchanged when exposures at home, at work, and in other settings were examined separately. The odds ratios were highest for exposure in other settings, but they were based on a small number of positive responses. There was no consistent pattern by histologic type. Squamous cell carcinoma showed the strongest relationship with involuntary smoking, based on the husbands' smoking habits at home (RR 5.0, 95 percent C.I. 1.4, 20.1), but failed to show any relationship when involuntary smoking exposure was classified by hours of daily exposure.

This case–control study has the largest number of nonsmoking lung cancer cases to date and provides estimates of the misclassification of disease and of the smoking status of the subjects. Among the published studies on involuntary smoking, this is the only one involving independent verification of the diagnoses of all cases. This verification showed that 13 percent of the cases classified as lung cancer were not primary cancers of the lung. This study showed that 40 percent of the women with lung cancer who had been classified as nonsmokers (or smoking not stated) on hospital records had actually smoked, compared with 9 percent of the controls. The inclusion of lung cancer patients who had actually smoked would have substantially increased the odds ratios with involuntary smoking, because 81 percent of the potentially misclassified cases had husbands who smoked compared with 68 percent of the "true" nonsmoking patients with lung cancer. It should be noted that none of the other studies on involuntary smoking and lung cancer based classification of smoking status solely on data from medical records. The measure of involuntary smoking based on smoking habits of husbands attempted to differentiate between current total smoking habits and current smoking habits at home. The interview also included ETS exposure not only at home but at work and in other settings.

The exposure information presented in this study is potentially limited by its extensive reliance on surrogate interviews. Owing to the need to assemble sufficient nonsmoking cases, diagnoses as early as 1971 were included, so proxies were interviewed for a high percentage of the deceased cases. Among the cases, 12 percent of the interviews were conducted with the subject, 25 percent with the husband, 36 percent with offspring, and 27 percent with an informant who had known the subject for at least 25 years. The corresponding distribution of informants in the control series was not presented. Although the ORs did not vary consistently by respondent group, the OR for smoke exposure based on the husbands' smoking tended to be lower when husbands were the respondents. Presumably, the husbands reported their own smoking habits, and it cannot be determined whether bias resulted. The information provided by surrogates may be particularly inaccurate for exposures outside the home. Systematic bias between personal and surrogate interviews and systematic bias by informant status must also be considered. Given that the topic of involuntary smoking is potentially sensitive for the family of a lung cancer patient, it is possible that some surrogates may not have provided accurate histories, particularly with regard to their own smoking habits. Surrogate respondents for cases might have been more likely to underreport exposure than those for controls; such differential reporting would have led to an underestimation of the true effect. The multiple regression analysis performed in this study did take

respondent status into consideration, and it was determined that this factor could not account for the relationship with husband's smoking status (Garfinkel et al. 1985). It is not clear if the colorectal cancer controls were diagnosed in the same years as the lung cancer cases. Because the response patterns of relatives who are interviewed after the recent death of a subject may differ from responses obtained long after the subject has died, another source of bias may have been introduced.

A United Kingdom Study

In an ongoing hospital-based case–control study of lung cancer, chronic bronchitis, ischemic heart disease, and stroke, Lee and colleagues (1986) examined the role of involuntary smoking in a group of inpatients interviewed after 1979, when, to cover involuntary smoking, the questionnaire was extended to married patients. An attempt was also made to interview the spouses of the married nonsmoking lung cancer patients and the spouses of the comparison group.

The interview on involuntary smoking administered to hospital inpatients included questions on the smoking habits of their first spouse and on ETS exposure at home, at work, during travel, and during leisure, based on a subjective four-point scale. Spouses of nonsmokers were asked about their own smoking habits at the time of interview, during the year of admission of the subject, and during the course of their marriage.

A total of 56 lung cancer cases among married lifelong nonsmokers was identified; 2 controls were selected for each case and individually matched on nonsmoking status, sex, marital status, age, and hospital. Among the 56 cases and 112 controls, information on spouses' smoking habits was available for 29 (52 percent) cases and 59 (56 percent) controls from an interview conducted while the patient was still in the hospital. Interviews with spouses were obtained for 34 (61 percent) of the cases and 80 (71 percent) of the controls. Using both of these sources of information, the smoking habits of spouses were available for 47 (84 percent) of the cases and 96 (86 percent) of the controls. Nine risk estimates were presented for spouses' smoking, for each of the three sources of information (subject, spouse, and both), for men and women separately and for both sexes combined. The researchers concluded that spousal smoking was not associated with lung cancer, because risks were not consistently elevated. When their spouses reported about their own smoking, a RR of 1.60 (95 percent C.I. 0.44, 5.78) was found for lung cancer in the women. In contrast, a RR of 0.75 (95 percent C.I. 0.24, 2.40) was found when the female subjects reported about the smoking habits of their spouses. On the other hand, a RR of 1.01 (95 percent C.I. 0.23, 4.41) was found for male lung cancer patients when

their spouses reported about their own smoking, whereas the risk was 1.53 (95 percent C.I. 0.37, 6.34) when the male patients evaluated their spouses' smoking habits. As might be expected, the combined risk in relation to spouses' smoking for both sexes and both sources of information was near unity, at 1.11 (95 percent C.I. 0.59, 2.39). Using a second group of controls, presumably all of the nonsmokers who had responded to the hospital inpatient interview on involuntary smoking, the researchers reported no significant case and control differences in exposure to ETS at home, at work, during travel or leisure, from spouses, or for all sources combined.

This study has several limitations that must be considered in interpreting its results. Although the study attempted to verify involuntary smoking from spouses by using two sources of information, dual reports were obtained for only 16 (29 percent) of the cases and 43 (38 percent) of the controls. The questions on involuntary smoking included exposure from other sources, but they were based on a subjective scale, and different groups of controls were used for the analyses. Information was not presented on the accuracy of the diagnosis of lung cancer or on the histological types included in the study. Moreover, the investigators did not verify the smoking status of the subjects during the interviews with spouses.

The study's inconsistent findings by source of information and by sex may reflect the absence of an association between involuntary smoking and lung cancer in this population, or may reflect methodological problems in the design or conduct of the study. The main study was not originally designed to investigate the effects of involuntary smoking. However, because of interest in this issue, the investigators decided to "increase the number of interviews of married lung cancer cases and controls." The representativeness of the cases and the controls cannot be determined because there may have been differential selection factors in enrolling nonsmoking lung cancer cases and controls into the study; thus, selection bias cannot be ruled out. The method for selecting the 112 nonsmoking controls was not adequately described in the report; it is not clear whether they were selected from the pool of all controls for lung cancer or from the pool of controls for the four diseases under study. There is also an apparent discrepancy in the number of nonsmoking cases cited in the text and presented in the results. The report cited 44 never smokers among a total of 792 lung cancer patients who completed the involuntary smoking questionnaires when they were in the hospital. However, the analysis for an involuntary smoking effect based on interviews with subjects in the hospital showed only 29 lung cancer patients. This discrepancy was not explained.

The risks in relation to smoking by spouses varied with the source of information. The risk estimates tended to be higher when the respondents were men, either reporting about their own smoking

habits or the smoking habits of their spouses. This pattern could result if the male respondents overestimated exposure to environmental tobacco smoke or if the female respondents underestimated exposure. An analysis of the patients (16 cases and 43 controls) for whom data were provided by the spouses and by the subjects themselves showed a 97 percent concordance for spouses' smoking during the year of the interview and 85 percent concordance for spouses' smoking some time during the marriage. Lack of specificity in the question asked regarding spouses' smoking any time during the marriage may partly explain the discrepancy in response. To the extent that there is no consistent pattern in the direction of this discrepancy, it can be assumed that a spouse was a smoker sometime during the marriage if either respondent answered positively. On the basis of this assumption, RRs of 1.47 (spouses of 4 of 7 cases and 7 of 18 male controls smoked) and 1.39 (spouses of 8 of 9 female cases and 16 of 25 female controls) were found for the men and the women, respectively, in relation to their spouses' smoking. The risk estimates were not statistically significant, but the number of subjects was small.

The Japanese Case–Control Study

The study by Akiba and colleagues (1986) included 428 (264 men, 164 women) incident primary lung cancer cases diagnosed between 1971 and 1980 in a cohort of 110,000 Hiroshima and Nagasaki atomic bomb survivors. Controls were selected among cohort members who did not have cancer. For deceased cases, corresponding controls were selected from among cohort members who died of causes other than cancer or chronic respiratory disease. The controls were individually matched to cases on a number of factors, including age, sex, birth year (± 2 years), city of residence, and vital status; a variable number of controls was interviewed, depending on the place of residence. Of the lung cancers, 29 percent were pathologically confirmed, 43 percent were radiologically or clinically diagnosed, and the remainder were found at autopsy.

Subjects or their next of kin were interviewed regarding the subjects' personal smoking, smoking habits of current spouses and parents, and occupation. Less than 10 percent of the interviews with the men and about 20 percent of the interviews with the women were conducted with the subjects themselves. The distributions of the next of kin interviewed were similar for the cases and the controls.

Among the cases, 103 (19 men, 84 women) had never smoked, compared with 380 controls (110 men, 270 women). An elevated lung cancer risk associated with smoking habits of spouses was observed for men and women. An OR of 1.8 (95 percent C.I. 0.5, 5.6) was found for nonsmoking men married to wives who smoked and an OR of 1.5

(95 percent C.I. 1.0, 2.5) for nonsmoking women married to husbands who smoked. Lung cancer risk increased with the amount smoked per day by the husband, with an OR of 2.1 for women whose husbands smoked 30 or more cigarettes per day. The OR was higher (1.8) among women who had been exposed within the past 10 years compared with those who had been exposed before that time (OR 1.3). However, an increasing duration of exposure to husbands' smoking was not associated with a monotonic trend of increasing risk. The relation between lung cancer and husbands' smoking was observed regardless of the occupation of wives (housewife, white-collar, blue-collar), but the highest odds ratio was for women who worked in blue-collar jobs and whose husbands were heavy smokers (OR 3.2).

Despite a high proportion of proxy interviews, the distribution of informant type was comparable for cases and controls; this comparability minimizes the possibility of recall bias. The high concordance between the subjects' reported smoking status in a previous survey and the information from the next of kin is reassuring. Although a high proportion of cases had no histological confirmation, an increased risk was observed regardless of the method of diagnosis. This study also provided an opportunity to test for potential confounding factors, including radiation exposure and occupation, but none were identified.

The Swedish Study

The study by Pershagen and associates (in press) included 67 incidents of primary lung cancer cases from a cohort of 27,409 nonsmoking Swedish women who were participants in a national census survey or in a twin registry. Two controls were selected from each source and were matched to cases on year of birth, and on vital status if they were selected from the twin registry.

Subjects or their next of kin (excluding husbands) were mailed a questionnaire that assessed their exposure to tobacco smoke from parents and the husband with whom the subject had lived the longest time. Information on residential and occupational history was also obtained.

Elevated lung cancer risk associated with the smoking habits of spouses was observed. For all lung cancers, ORs of 1.0, 1.0, and 3.2 were observed for women who had no, low (≤ 15 cigarettes/day or <1 pack of pipe tobacco/week or <30 years of marriage), and high exposure to their husbands' smoking, respectively. The increased risk was found primarily for squamous and small cell carcinomas (OR 3.3); consistent effects could not be detected for other histologic types. On the basis of the approximately 75 percent of respondents who provided information on parental smoking, there was no effect

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of parental smoking on risk for all lung cancers, after controlling for the husbands' smoking.

The study is similar in design to the Japanese case–control study (Akiba et al. 1986), except that the Swedish investigators obtained histologic confirmation for all of the cases under study. Moreover, this study excluded husbands as informants, so a potential bias associated with husbands' reporting their own smoking habits could be eliminated. The investigators contended that the finding of an association only for squamous cell and small cell carcinomas argues against a spurious finding because it is unlikely that the next-of-kin informers would have been aware of the histologic types diagnosed in the cases.

The German Study

The last in this description of studies to date based on the case–control design is a German study (Knoth et al. 1983), interpreted by the investigators as showing a role for involuntary smoking in the etiology of lung cancer. Of 39 nonsmoking women with lung cancer, 24 (62 percent) had lived with smokers. Although a comparison group was not interviewed, the investigators surmised that this frequency of smokers in the household was about three times higher than expected from census-based smoking statistics for men in the age group 50 to 69. The limitations of this study are evident; the researchers assumed that smoking prevalences for men were indicative of smoking prevalences for members of the cases' households and a specific control series was not enrolled.

Other Sources of Tobacco Smoke Exposure

Parental Smoking

Recently evaluated as a risk factor for lung cancer, parental smoking is of interest because of the large number of exposed children, the age at which it begins, and its duration. Results of this association are variable, demonstrating no association, association with just mothers' smoking, or association with both mothers' and fathers' smoking. Correa and colleagues (1983) reported an association between lung cancer risk and the mothers' smoking in the men, which persisted after adjusting for personal smoking habits (OR 1.5, $p < 0.01$). This association was not observed in the women, and increased risk was not related to fathers' smoking in either the men or the women. A positive association between the mother's smoking and lung cancer risk was reported in a study of female lung cancer, but the result was not statistically significant after adjusting for personal smoking habits (OR 1.7, 95 percent C.I. 0.8, 3.5) (Wu et al. 1985). Another study suggested that the father's smoking (OR 2.5) and the mother's smoking (OR 1.8) were each related to increased

lung cancer risk after adjusting for age and individual smoking habits (Sandler, Wilcox, Everson 1985b). These results were based on small numbers, however, particularly for the mother's smoking (in 2 of 15 cases, the mother smoked). Significant associations with maternal or paternal smoking were not found in two other studies (Akiba et al. 1986; Pershagen et al. in press); however, information was lacking for about one-third of the subjects. Since smoking habits of children are highly correlated with smoking habits of parents, it is difficult, even after adjusting for personal smoking habits, to be certain that an independent effect of parental smoking has been observed.

None of the studies with data on parental smoking had sufficient numbers to examine the effects of parental smoking on nonsmokers. In Louisiana, one nonsmoking case had a mother who smoked (Correa et al. 1983). In Hong Kong, 6 percent (5/88) of the nonsmoking cases reported that their parents smoked compared with 2 percent (3/137) of the nonsmoking controls (Koo et al. 1984). In Los Angeles, the frequencies of smoking by mothers and fathers were lower for nonsmoking cases (4 percent mothers, 28 percent fathers) than for nonsmoking controls (11 percent mothers, 35 percent fathers) (Wu et al. 1985). Exposure to tobacco products during childhood was not significantly different between cases and controls (OR 0.91, 95 percent C.I. 0.74, 1.12) in another study (Garfinkel et al. 1985).

It is difficult to obtain accurate information regarding remote childhood events, so data on parental smoking tend to be crude or unavailable. Information on maternal smoking during pregnancy would not be available unless the parents could be interviewed. Because lung cancer occurs most often among older persons, an interview with a parent will generally be impossible. Moreover, information on parental smoking will most likely be unavailable or meaningless if surrogate interviews are conducted.

Coworker's Smoking

The workplace, an important source of tobacco smoke exposure, was not considered in the early studies on involuntary smoking. Later case–control studies provided some information on tobacco exposure at work, but the data were limited and inconclusive. Kabat and Wynder (1984) reported a statistically significant positive association between tobacco smoke exposure at work for men but not for women. In comparison with controls, patients with cancer in Hong Kong reported more hours and years of exposure at the workplace, but only two cases and four controls had exposure to tobacco smoke at work (Koo et al. 1984). Data in the Los Angeles study suggested that the workplace may be an important source of exposure to tobacco smoke. A small increased risk was observed for

any exposure at work, and an index combining exposure from coworkers and spouse or spouses indicated a trend of increasing risk with increasing exposure (Wu et al. 1985). Garfinkel and colleagues (1985) found no differences between cases and controls in their exposure to tobacco smoke at work during either the 5 years or the 25 years before diagnosis, and a similar lack of an association was also reported by Lee and colleagues (1986).

Dose-Response Relationship

An important factor in the appraisal of the relationship between involuntary smoking and lung cancer is the assessment of dose–response relationships. However, this analysis hinges on the definition of exposure. Data on active smoking and lung cancer suggest that exposure measures considering amount, duration, and recency of exposure should be employed in examining dose–response relationships in active smokers (Doll and Peto 1978; Pathak et al. 1986). Misclassification of exposure to ETS may be expected when exposure categorization is based on the amount or the duration of smoking by the current spouse or cohabitant, as current exposure from one source may not adequately measure past exposure or cumulative exposure. Moreover, these exposure variables may not be indicative of the exposure dose to the respiratory tract because dose determinants such as ventilation rates, breathing pattern, and deposition factors are unaccounted for.

Research is now being directed toward the integration of information from questionnaire responses, biochemical studies, and environmental sampling to determine the most accurate measures of exposure to the respiratory tract. However, exposure assessments for epidemiological studies of lung cancer and involuntary smoking will remain limited by the inaccurate recall of exposures that occurred as much as 40 to 50 years earlier. Nevertheless, research on exposure should resolve several points of uncertainty. The comparability between exposure dose measured by amount smoked and by hours or years of smoking should be assessed. The relative importance of sources of ETS should also be clarified, so there will be some agreement on whether cumulative dose should differentiate between sources of exposure.

In the absence of data showing a particular exposure measure to be optimal, an index of involuntary smoking based on the amount smoked by spouses shows the most consistent dose–response relationship with lung cancer risk (Hirayama 1981a; Trichopoulos et al. 1981; Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986). Other indices of involuntary smoking exposure have not been as well studied and have not shown a consistent dose–response relationship with lung cancer risk. These exposure variables included total years of exposure to spouses' smoking, average daily hours of exposure

from all sources, and cumulative lifetime hours and years of exposure.

Among the studies that have found a dose–response relationship with amount smoked by a spouse, three have also examined the relationship by duration of spouse's smoking (Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986), but only one study showed similarly increased risk using a dose and duration variable (Correa et al. 1983). In the study by Garfinkel and coworkers (1985), only years of smoking by the current husband or cohabitant was asked; therefore, differences in the duration of living with current husband or cohabitant may account for the less consistent dose–response relationship. In their Japanese case–control study, Akiba and colleagues (1986) suggest that intensity (amount smoked per day and recency of exposure) may be the key index of ETS in studies of lung cancer risk.

Two studies have assessed total involuntary smoking exposure to ETS. The method used by Koo and coworkers (1984) relied on respondents to describe the exposures from each source separately, and a summary measure of exposure was derived by the investigators. The method used by Garfinkel and coworkers (1985) relied on the respondents to average their exposures from all sources for specific time periods. The method of Koo and coworkers (1984) may not have adequately considered intensity of exposure; therefore, an association may have been obscured by combining low and high intensity exposures as if they were equally important. In the study by Garfinkel and coworkers (1985), a high percentage of case interviews and, presumably, control interviews was conducted with surrogates. Although information provided by surrogates regarding demographic variables is generally valid, as are responses on cigarette smoking status (current, prior, never), more detailed information on the cigarette smoking of a deceased spouse has more limited validity (Lerchen and Samet 1986). Surrogate interviews may provide adequate information about tobacco smoke exposure at home, but may be inaccurate for describing gradients of total tobacco smoke exposure from all sources.

Expected Lung Cancer Risk

An extensive data base describes the relationship between active smoking and lung cancer (US DHEW 1979, US DHHS 1982; IARC 1986). This information has been utilized to construct mathematical models to describe the relationship of dose, duration, initiation, and cessation of active smoking for risk of lung cancer. For several reasons, comparable models have not yet been developed for involuntary smoking and lung cancer. First, research on involuntary smoking and lung cancer is recent. Second, involuntary smoking is not as readily quantified as active smoking; tobacco smoke is

ubiquitous in the environment and present in variable but generally low concentrations in comparison with MS, and inhaled dose varies with ventilation and other physiological factors (Hiller 1984; Hoegg 1972; Hoffmann et al. 1984; Schmeltz et al. 1975; Stöber 1984; US DHHS 1984).

Nevertheless, theoretical models, originally developed to describe the relationship of active smoking and lung cancer, have been used to predict lung cancer risk from involuntary smoking. Using Doll and Peto's (1978) model [(0.273 x 10^{-12}) (cigarette/day + 6)^2 (age 22.5)$^{4.5}$] for active smoking and lung cancer, Vutuc (1984) calculated expected lung cancer risks for various exposure levels, ranging from 0.1 to 5.0 cigarettes per day. For exposure levels of 0.1, 1.0, 2.0, and 5.0 cigarettes per day, the corresponding risk estimates were 1.03, 1.38, 1.78, and 3.36, respectively. These low-dose active smoking risk estimates are comparisons of active smokers with all nonsmokers (those with high ETS exposure and those with low ETS exposure). The risk estimates in involuntary smoking studies are a comparison of nonsmokers with higher levels of involuntary smoking exposure with nonsmokers who have lower levels of involuntary smoking exposure. As a result, the numerical values of the risk estimates in active smoking studies are not directly comparable to those in the involuntary smoking studies.

The appropriateness of extrapolating from the active smoking model hinges on the actual exposure of a nonsmoker. Estimates of exposure have been derived from various sources. Experimental conditions have been used to quantify the involuntary smoker's exposure to ETS. Hugod and colleagues (1978) reported that under conditions heavily polluted with sidestream smoke (to maintain a carbon monoxide concentration of 20 ppm), the particulates of tobacco smoke inhaled by involuntary smokers was small, the equivalent of one-half to one cigarette per day. Exposures may also be estimated from biochemical measurements. Studies comparing cotinine levels in nonsmokers and smokers show cotinine levels in nonsmokers that correspond to about one-sixth to one-third of a cigarette per day (Jarvis et al. 1984; Wald et al. 1984). Higher cotinine levels in nonsmokers, comparable to about two cigarettes per day, have been reported (Matsukura et al. 1984, 1985), but the results were questioned (Adlkofer et al. 1985; Pittenger 1985) and await confirmation.

The epidemiologic evidence on the lung cancer risk associated with marriage of a nonsmoker to a smoker has been criticized as implausible on the basis of predictions from Doll and Peto's model (Lee 1982a,b; Vutuc 1984). It has been argued that relative risks of 2 or 3 from involuntary smoking correspond to active smoking of two to five cigarettes per day and that this equivalent level of active smoking is too large to be realistic. This argument fails to consider

the difference in the comparison groups used to generate the risk estimates in studies of active smoking and involuntary smoking. The risk estimates for studies of active smoking use as a comparison group all nonsmokers, which includes those with and without high levels of exposure to ETS. Studies of involuntary smoking use risk estimates that are derived by comparing nonsmokers with higher levels of exposure to ETS with nonsmokers with lower levels of exposure to ETS. Because the risk estimates in active and involuntary smoking studies use different comparison groups, the numerical values are not directly comparable.

In order to make them comparable, the risk estimates in involuntary smoking and active smoking studies would have to be calculated using the same reference group. If the reference population used is all nonsmokers, then the risk estimates for nonsmokers married to nonsmokers are reduced to below 1 (i.e., their lung cancer risk would be lower than the risk for all nonsmokers as a group). The risk estimates for nonsmokers married to smokers would be above 1 (i.e., would be greater than the risk for all nonsmokers as a group), but the numerical value of the risk estimate would be reduced from th value obtained by comparison with nonexposed nonsmokers.

If the data from the Japanese cohort study (Hirayama 1981a) ar recalculated to use all nonsmokers as the reference population, the risk estimate for lung cancer in nonsmoking wives of nonsmoking husbands would be 0.63 and the risk estimate for nonsmoking women married to smokers (current or former) would be 1.12. The value of 1.12 compares the risk for nonsmoking wives of smoking husbands with the risk for all nonsmokers in the studies of active smoking. This magnitude of risk is within the range of risk that would be predicted using the Doll and Peto (1978) model for calculating active smoking risk for smokers of 0.1 (risk estimate 1.03) and 1 (risk estimate 1.38) cigarette per day. The evidence for exposure to environmental tobacco smoke based on biologic markers of tobacco smoke exposure indicate that involuntary smoking exposure results in levels of biologic markers (e.g., cotinine) that are similar to levels expected in smokers of 0.1 to 1 cigarette per day. Thus, estimates derived using similar comparison groups suggest that the lung cancer mortality experience due to involuntary smoking is similar to that which would have been expected from an extension of the dose–response data for active smoking to involuntary smoking exposures.

An alternative method of estimating expected lung cancer rates has been proposed by Repace and Lowrey (1985). They compared the age-standardized lung cancer mortality rates of Seventh-Day Adventists (SDAs) who had never smoked with a demographically comparable group of nonsmoking non-SDAs and attributed the difference in lung cancer deaths solely to involuntary smoking. This

analysis was based on the following assumptions: (1) that SDAs had no exposure to passive smoking, whereas all of the non-SDAs were exposed, (2) that men and women had equal lung cancer death rates, and (3) that there were no other differences between the two groups.

Summary

Previous Reports of the Surgeon General have reviewed the data establishing active cigarette smoking as the major cause of lung cancer. The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream smoke and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer.

The quantification of the risk associated with involuntary smoking for the U.S. population is dependent on a number of factors for which only a limited amount of data are currently available. The first of these factors is the absolute magnitude of the lung cancer risk associated with involuntary smoking. As was previously described, the studies that have been performed to assess the lung cancer risk of involuntary smoking do not contain a zero-exposure group. Some exposure to tobacco smoke is essentially a universal experience; therefore, studies of involuntary smoking compare a low-exposure group with a high-exposure group. The magnitude of the risk estimate obtained is a function of the increase in risk produced by the difference in tobacco smoke exposure between the two groups examined, rather than an absolute measure of the risk of exposure in comparison with no exposure. The magnitude of the difference in tobacco smoke exposure between groups identified by spousal smoking habits may vary from study to study; this variation may partially explain the differences in risk estimates among the studies. The extrapolation of the risk estimate data to the U.S. population would therefore require a better understanding of the magnitude of the exposure to environmental tobacco smoke that occurs in the populations examined in the studies of involuntary smoking and lung cancer. Of particular interest is the magnitude of the difference in exposure between the high-exposure group and the low-exposure group.

A second set of data that would be needed to estimate the risk for the U.S. population is the dose and distribution of exposure to ETS in the population. The studies that have been performed have attempted to identify groups with different exposures, but little is known about the magnitude of the exposures that occur in different segments of the U.S. population or about the variability of exposure with time of day or season of the year. The changing norms about

smoking in public and the changing prevalence of active smoking during this century suggest that ETS exposure may have varied substantially over this century. A better understanding of the exposures that are actually occurring in the United States, and of past exposures, would be needed to accurately assess the risk for the U.S. population.

The epidemiological evidence that involuntary smoking can significantly increase the risk of lung cancer in nonsmokers is compelling when considered as an examination of low-dose exposure to a known carcinogen (i.e., tobacco smoke). Eleven of the thirteen epidemiological studies to date show a modest (10 to 300 percent) elevation of the risk of lung cancer among nonsmokers exposed to involuntary smoking; in six studies positive associations were statistically significant. The studies showing no or nonsignificantly positive findings were generally the weakest in terms of sample size (Gillis et al. 1984; Chan and Fung 1982; Koo et al. 1984; Kabat and Wynder 1984; Wu et al. 1985; Lee et al. 1986), study design (Kabat and Wynder 1984; Lee et al. 1986), or quality of data (Chan and Fung 1982).

In Table 10 are shown the sources and types of bias, and in Table 11, the statistical power, of the various case–control studies (Schlesselman 1982). On the basis of the observed relative risks reported in the studies, the respective exposure fraction in the control populations, and an $\alpha=0.05$ for a two-sided significance test, only the studies by Trichopoulos and colleagues (1983) and Correa and colleagues (1983) have a probability of above 80 percent of finding a statistically significant result, whereas the majority of the case–control studies show a study power of about 0.10 to 0.20. The power of the study, as expected, improves when a one-sided significance test is considered. Among the studies in which information on involuntary smoking was available to conduct a trend test for dose, the power for detecting the observed trend was above 50 percent for five of the studies. However, the power for a two-sided test and a one-sided test, based on observed relative risk, and the power for a one-sided trend test, based on observed results, are difficult to interpret because the power is a function both of design aspects (sample size, case–control ratio, exposure prevalence) and of the observed relative risk. To focus on comparisons of the design differences between studies, the power estimates for a fixed relative risk of 2 show that five of the studies would have a power of 0.75 or greater to detect a statistically significant result. Thus, it is not surprising that some studies failed to achieve statistical significance, but the lack of statistical significance in all studies should not invalidate the positive significant associations for involuntary smoking that have been observed.

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TABLE 10.—Sources and types of bias in case-control studies

Study	Author's conclusion	Misclassification of lung cancer	Misclassification of passive smoke exposure	Interviewer bias	Respondent bias
Trichopoulos et al. (1983)	Positive	+ (↓)	+ (↓)	+ (↑)	—
Correa et al. (1983)	Positive	—	+ (↓)	—	—
Chan and Fung (1982)	Negative	—	+ (↓ or ↑)	?	?
Koo et al. (1984)	Negative	—	+ (↓ or ↑)	?	?
Kabat and Wynder (1984)	Negative	—	+ (↓ or ↑)	?	?
Wu et al. (1985)	Weak positive		—	+ (↑)	—
Garfinkel et al. (1985)	Positive	—	+ (↓ or ↑)	—	+ (↓ or ↑)
Akiba et al. (1986)	Positive	+ (↓)	+ (↓)	?	+ (↓ or ↑)
Pershagen et al. (in press)	Positive	—	+ (↓ or ↑)	—	—

NOTE: Probability of misclassification: + = likely; — = not likely; ? = cannot be determined. Effect on observed risk: ↑ = overestimated risk as result of bias; ↓ = underestimated risk as result of bias.

Six epidemiological studies found statistically significant increased risks associated with spouse's smoking; all demonstrated a dose-response relationship, and several suggested a stronger association with squamous cell and small cell carcinoma than with other cell types. Three of these studies (Hirayama 1984a; Correa et al. 1983; Akiba et al. 1986) included nonsmoking male lung cancer patients, and the complementary findings in nonsmoking husbands married to smoking wives strengthen the evidence on involuntary smoking. The four studies with significant positive findings published since 1981 (Correa et al. 1983; Garfinkel et al. 1985; Akiba et al. 1986; Pershagen et al., in press) not only corroborated the findings of Hirayama (1981a) and Trichopoulos and colleagues (1981), but answered the many criticisms directed at these two studies.

TABLE 11.—Study power for case-control study based on an unmatched analysis

Study	Number of cases	Control: case ratio	Proportion of controls' spouses who smoked	Observed relative risk for ever vs. never exposed to spouses' smoking	Power for two-sided test based on observed RR	Power for one-sided test based on observed RR	Power for one-sided trend test based on observed results[1]	Power for one-sided test based on RR=2 for ever vs. never exposed
Trichopoulos et al. (1983)	77	2.92	0.52	2.11	0.79	0.87	0.88	0.88
Correa et al. (1983)	30	10.43	0.28	2.97	0.83	0.88	0.97	0.55
Chan and Fung (1982)	84	1.66	0.48	0.75	0.17	0.26	NA[2]	0.80
Koo et al. (1984)	88	1.56	0.71[3]	1.23	0.10	0.17	0.10	0.64
Kabat and Wynder[4] (1984)	36	1.03	0.54	0.85	0.05	0.10	NA[2]	0.39
Wu et al.[5] (1985)	28	1.96	0.60	1.41	0.10	0.17	0.16	0.37
Garfinkel et al. (1985)	134	3.00	0.61	1.23	0.24	0.36	0.71	0.94
Lee et al. (1986)	47	2.04	0.62	1.11	0.04	0.08	NA[2]	0.52
Akiba et al.[6] (1986)	84	2.96	0.67	1.47	0.26	0.38	0.53	0.75

TABLE 11.—Continued

Study	Number of cases	Control: case ratio	Proportion of controls' spouses who smoked	Observed relative risk for ever vs. never exposed to spouses' smoking	Power for two-sided test based on observed RR	Power for one-sided test based on observed RR	Power for one-sided trend test based on observed results[1]	Power for one-sided test based on RR=2 for ever vs. never exposed
Pershagen et al. (in press)	67	5.18	0.44	1.23	0.12	0.19	0.46[7]	0.83
Pooled[8]	676	2.96	0.52	1.53	0.99	1.00	NA	1.00
Pooled[9]	509	3.40	0.52	1.88	1.00	1.00	1.00	1.00

[1] Based on three levels of passive smoke exposure as defined in respective studies.
[2] Data not available for trend test.
[3] Includes spouses, cohabitants, and coworkers who smoked.
[4] Based on nonsmoking cases and controls with information on spouses' smoking.
[5] Based on cases and controls who were ever married.
[6] Based on female cases and controls with information on husbands' smoking (number of cigarettes smoked per day).
[7] Estimate based on 26 cases and 151 controls in the low exposure category, 7 cases and 12 controls in the high exposure category.
[8] Based on combined results of the 10 case–control studies.
[9] Based on combined results of the seven case–control studies with data available for trend test.