ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER

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Kenneth G. Brown

Douglas J. Crawford-Brown

with

Charles G. Humble

Chu-Chih Chen

Kenneth G. Brown, Ph.D.

310 Carl Drive
Chapel Hill, NC 27516
(919) 933-0789

• ***Research Statistics*** • ***Health Effects Assessment*** •

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1. INTRODUCTION AND SUMMARY

In early 1981, the results of a case control study undertaken in Greece to explore the relationship between lung cancer and passive smoking reported a significant increase in lung cancer among nonsmoking women married to smokers (Trichopoulos, 1983). Almost simultaneously, similar results were reported from a methodologically different cohort study in Japan (Hirayama, 1981). Within the year, results from the cohort study of the American Cancer Society appeared (Garfinkel, 1981). Evidence from the American study was equivocal, but not incompatible with conclusions of the previous two studies. These events in 1981 were probably the genesis of what a recent expert panel convened by the International Agency for Research on Cancer (IARC) has described as the most actively investigated segment of the whole smoking *versus* health domain of research during the eighties – environmental tobacco smoke and lung cancer (Sarracci, 1989).

Three factors that contribute to the relevance of exposure to environmental tobacco smoke (ETS) for public health include: (1) the ubiquity of ETS, as evidenced by experimental measurements of airborne concentrations in public places and the presence of tobacco-specific biological markers, such as cotinine, in nonsmokers; (2) the involuntary aspect of exposure to ETS, in contrast to active smoking; and (3) the biological plausibility of lung cancer risk from ETS, based on the identification of carcinogens in ETS and the lack of convincing evidence of a threshold tolerance level.

Additional epidemiologic studies in the early 1980s continued to fuel concern about potential health risks from ETS, with lung cancer risk probably receiving the most attention, while discrepant conclusions and controvertible methods fueled controversy. In the mid-1980s, the U.S. Surgeon General, the National Research Council, and IARC all

convened scientists to consider the evidence of health risks associated with exposure to ETS. As discussed by Samet (1988), all three groups concluded that ETS exposure is associated with an increased risk of lung cancer, although they used somewhat different approaches. The U.S. Surgeon General (S.G., 1986) concluded that passive smoking is a cause of lung cancer, based on (1) the evidence that active smoking is a risk for lung cancer, (2) the qualitative similarities between ETS and mainstream smoke, and (3) the epidemiologic evidence. The National Research Council (NRC, 1986) considered the biological plausibility of lung cancer from ETS and emphasized the epidemiologic evidence. After an overall analysis of the data for ten case control and three cohort studies, and carefully considering potential sources of bias (bias due to misclassification, in particular), it was concluded that there is a positive association between ETS and lung cancer. The International Agency for Research on Cancer (IARC, 1986) reviewed the evidence available through the end of 1984 and emphasized issues related to the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. The report quotes the summary statement on passive smoking of a previous IARC working group that found the epidemiological evidence available at that time (1985) compatible with either the presence or absence of a lung cancer risk. Based on other considerations related to biological plausibility, however, it was concluded that passive smoking gives rise to some risk of cancer.

At the present time there are 21 case control studies suitable for analysis of a lung cancer risk associated with ETS exposure. No additional cohort studies have appeared. The more recent case control studies are described in the appendix of this report. In Chapter 2 the weight of observational evidence of a lung cancer risk is statistically assessed using the large number of studies on ETS currently available. The data are analyzed from several perspectives, with consistent results.

Conclusion 1: Based on analysis of epidemiological data, the occurrence of lung cancer deaths in females classified as never smokers is positively associated with spousal smoking. The weight of statistical evidence virtually precludes the possibility of occurrence by chance.

Once a hazard has been identified, it is of interest to have some idea of the magnitude of risk to the population. A tractable measure is the number of excess lung cancer deaths (LCDs) associated with ETS exposure, often called the "population attributable risk". The population in this case consists of U. S. women who are never smokers of age 35 or above. Estimates in the literature can be classified under two approaches: "cigarette equivalent", where ETS exposure is considered equivalent in risk to some specified level of light active smoking, and "epi-data", where the data from epidemiologic data are utilized but no equivalence is made with active smoking. Several authors have found the cigarette approach contentious. A biokinetic model has been developed to shed some light on the biologically-based similarities and differences between passive and active smoking that may affect lung cancer risk. That topic is reviewed next, followed by estimation of excess LCDs.

Passive and active smoking differ in a number of ways that may affect lung cancer risk. ETS and mainstream smoke (MSS) differ in chemical constituency, with a wide range in the relative concentrations of possible carcinogens. Exposure to ETS in passive smoking and exposure to MSS in active smoking differ profoundly in terms of concentration and temporal pattern of exposure. There is a wide range of variability in exposure to ETS in nonsmokers alone, with the added complexity of an aging effect on characteristics of ETS. For example as ETS ages, the proportion of tar in the vapor phase increases to about 70% (Pritchard et al., 1988) which may impact carcinogenic risk. This contrasts with active smoking where all of the tar is in the particulate phase.

The distribution of a chemical between the vapor and particulate phases affects integral lung burden from both passive and active exposure (i.e., ETS exposure to nonsmokers and MSS exposure to active smokers). In particular, the lung uptake and deposition by lung region of a chemical in the particulate phase is largely influenced by the distribution of the diameter and density of particulates to which the chemical attachs. Chemical-specific characteristics are major determinants of dosimetry parameters for a chemical in the vapor phase. ETS and MSS are complex mixtures of chemicals, with a large number of identified (or suspected) carcinogens in common. The relative presence of the chemicals in ETS and MSS (measured as a percentage of total mass) varies widely across chemicals. Furthermore, the distribution of a chemical between the vapor and particulate phases may differ for ETS and MSS.

The quantitative model derived in Chapter 3 relates exposure to any chemical constituent of tobacco smoke (ETS or MSS) to integral lung burden and translocation to systemic organs. It identifies parameters and their inter-relationships that distinguish between active and passive smoking, the vapor and particulate phases, and major regions of the lung (naseopharyngeal, tracheobronchial, and pulmonary). A number of possible exposure measures to a given chemical in ETS are suggested that require increasing levels of knowledge regarding biokinetic parameters. Calculations are demonstrated for nicotine and cotinine.

While the precise meaning of "dose", and particularly "biologically significant dose", has not been established in the literature, most theories rely on some measure of organ burden or integral organ burden as a measure of the rate or probability of transition in a multistage process. This implies that the burden of a chemical in each cellular subpopulation connected causally to lung cancer must be specified in order to make accurate biologically-based predictions of risk. This is a severe requirement, compounded by incomplete knowledge of which chemicals in ETS are the major contributors to lung

cancer risk. This complexity makes exploration of potential dose surrogates attractive. Two measures that have been suggested as dose surrogates for risk assessment are cotinine and respirable suspended particulates (RSP). Lung burdens for RSP and nicotine/cotinine can be approximated. There is no support, however, for the assumption that burdens from other chemicals in ETS (for which biokinetic parameters are not available) will scale according to relative intakes.

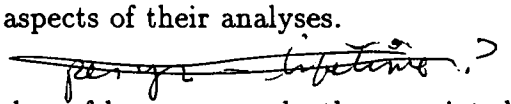
Conclusion 2: Lung burdens cannot be calculated for most chemicals in ETS, even the most significant ones. The major lack of data concerns the solubilization of chemicals from respirable suspended particulates into lung tissue and the uptake of vapor phase components. While limited data on clearance of RSP and nicotine from the lung are available, retention functions for other chemicals are unavailable. As a result, it is not possible to develop a surrogate measure of dose for chemicals existing simultaneously in the vapor and particulate phases.

Conclusion 3: Even if lung burdens of all chemicals could be estimated, their individual effects may be delivered to differing cellular subpopulations. Since the doses to cellular subpopulations can differ dramatically within the lung, development of biologically meaningful surrogates of dose must be tied to identification of the causal roles of the various chemicals. This link is not available at present.

Conclusion 4: Any measure that is directly proportional to lung burden from exposure to ETS will serve as an adequate surrogate, provided it is proportional to burden in all important subpopulations of cells, and the proportionality ratios are invariant of ETS exposure concentrations, i.e., the proportionality ratios remain constant independent of variations in ETS exposure.

In Chapter 4. upper and lower confidence bounds (nominally 92%) are obtained for the proportion of lung cancer deaths (LCDs) in 1988 associated with ETS exposure. The population considered consists of U. S. female never smokers at least 35 years of age. The population of women is used because the epidemiologic evidence is predominantly for female never smokers and the data on males are relatively sparse. The confidence bounds, based on the case control studies currently available, are applied to the 6,500 LCDs in 1988 among U. S. women classified as never smokers (estimate from the American Cancer Society). The resultant confidence interval provides a range of values on the number of LCDs associated with ETS exposure, i. e., the population attributable risk, that is consistent with the epidemiologic evidence.

Estimates from the published literature are compared relative to the confidence interval. Five estimates are based on the cigarette equivalent approach. Two of the five equate risk from passive smoking to light active smoking based on relative cotinine levels found in active and passive smokers; one determines an equivalent level of light active smoking using RSP; the remaining two (by the same author) are hybrid procedures in which the results are expressed as a range of values depending on unknown parameter values. An additional five sources rely only on epidemiologic data (the epi-data approach). One of the five estimates is based on a set of data independent of the case control studies on ETS. The remaining four authors rely on case control studies for ETS, but differ in the studies utilized and in various aspects of their analyses.



Conclusion 5: The excess number of lung cancer deaths associated with ETS exposure in U. S. female never smokers in 1988 is very likely between 850 and 2,400. This range is based on an approximate 92% confidence interval derived from the results of sixteen case control studies of ETS exposure, including two studies with a negative estimate of attributable risk (below the parameter space [0,1]). The range has been increased by 20%

(based on the NRC report) to adjust for an estimated net effect from sources of bias.

Conclusion 6: Published estimates of the number of excess LCDs associated with ETS, standardized to a total of 6,500 LCDs, are largely consistent with the range 850 - 2,400. Four of the five sources using the epi-data approach are in the interval 1,300 - 1,900. The fifth is slightly below the range (800). Of the five estimates following the cigarette equivalent approach, the two based on cotinine concentrations are 1,800 and an interval estimate of 1,600 - 2,150, well within the confidence bounds and consistent with four of the five epi-data estimates. Results of the two hybrid methods are presented as plausible intervals, 1,650 - 3,000, and 550 - 3,000. The fifth estimate using the cigarette equivalent approach is based on exposure to RSP and is singularly small (5). It is the only aberrant result relative to the confidence interval.

Conclusion 7: The number of excess LCDs associated with ETS exposure in U. S. female never smokers in 1988 is conservatively about 1,500. The total for the whole U. S. population, including male never smokers and ex-smokers of both sexes, is difficult to assess. An additional increment of several hundred to the 1,500 is probably minimal. An increase on that order is consistent with the limited epidemiologic evidence for males alone. Unfortunately, data sources and biological knowledge regarding ETS exposure in former smokers are both insufficient, even for speculation.

The NRC report suggests that ETS may modify the risk of lung cancer from radon progeny in the home. Chapter 5 identifies eight possible risk-modifying effects and addresses the potential influence of each. The overall impact of ETS on the risk from radon progeny is quantified for an example home of specified characteristics (volume, air exchange rate, average smoking rate in the home).

Conclusion 8: ETS changes both the equilibrium fraction and the unattached fraction of

radon progeny, may change both the rate of mucous transport and mucous thickness, may cause the breathing pattern to shift to more frequent shallow breaths, and may interact synergistically with the radon progeny, increasing their effect.

Conclusion 9. Under the standard assumption that the unattached fraction of radon progeny contribute significantly to the lung dose, the net effect of ETS is a reduction in dose-rate from radon progeny to about three-fourths of the initial (smoke-free) value. The assumption, however, has been brought into question by very recent work suggesting that the unattached progeny may be mostly removed by the naseo-pharyngeal region during normal breathing (Swift et al., 1989). In that case, ETS would produce a small increase in dose-rate, instead of a net reduction.

Conclusion 10. Further research is needed to clarify the role of the unattached fraction in the production of the lung dose from airborne radon progeny in the home, since this factor determines whether ETS has a net effect of raising or lowering the risk from radon progeny. Additional research is also needed to define the initial particle concentrations in homes where ETS is likely to be produced, since the initial concentration is an important determinant of the influence of ETS on lung dose.

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2. EPIDEMIOLOGIC EVIDENCE OF LUNG CANCER FROM ENVIRONMENTAL TOBACCO SMOKE

2.1. CASE CONTROL STUDIES: BACKGROUND

A list of case control studies for evaluating whether there is an elevated lung cancer risk due to exposure to ETS, primarily in the home, is shown in Table 2-1. The studies are denoted by the first few letters in the name of the first author for easy reference. Additional descriptive characteristics of the studies are given in Tables 2-2, 2-3, and 2-4. The three cohort studies available (Hirayama, 1984; Garfinkel, 1981; and Gillis, 1984) are discussed separately in Sections 2.6 and 2.7.

The report of the National Research Council (NRC, 1986) reviews and analyzes ten of the studies shown in Table 2-1: AKIB, BUFF, CHAN, CORR, GARF, KABA, KOO, LEE, PERS, and TRIC. The study designated as WU in the table is excluded by the NRC because the raw data are not presented in the reference, a requirement of the statistical method used by the NRC to combine results across all studies (meta-analysis). The NRC excludes an earlier version of the KOO study, and the studies by Knoth et al. (1983), Miller (1984), and Sandler el al. (1985) for assorted reasons (NRC, 1986, p. 227). Aside from WU, these same studies are also omitted from this report. Also not included here is a small set of data on males in New Jersey that was pooled with the data from BUFF and CORR for analysis by Dalager et al. (1986). The data for the New Jersey males are not available separately, and the other two studies are included in this report.

The NRC, after carefully assessing the epidemiologic evidence from the three cohort studies and the ten case control studies listed above and then adjusting for

potential bias from misclassification, concludes that "The weight of evidence derived from epidemiologic studies shows an association between ETS exposure of nonsmokers and lung cancer that, taken as a whole, is unlikely to be due to chance or systematic bias." The Surgeon General's report on passive smoking (SG, 1986), based on the same epidemiologic studies except with WU included and BUFF omitted, concludes that "The epidemiologic 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)." The report of the International Agency for Research on Cancer (IARC, 1987) includes the three cohort studies above and nine case control studies in its assessment of passive smoking. The case control studies differ from the list for NRC by inclusion of Knoth et al. (1983) and WU, and omission of BUFF, PERS, LEE. The IARC report quotes the summary conclusion on passive smoking of an IARC working group, which met in February, 1985: "The observations on nonsmokers that have been made so far are compatible with either an increased risk from 'passive' smoking or an absence of risk". The reason that fewer case control studies are included in the work of IARC appears to be attributable to study availability. The IARC committee began meeting in 1984, even though the report did not appear in the IARC scientific publications until 1987.

Of the three major reports (NRC, SG, IARC), the NRC places the greatest emphasis on technical evaluation of the epidemiologic studies. In particular, it analyzes the raw data from each study and then combines the evidence across studies to estimate an overall relative risk with a confidence interval. A recent article by Wells (1988b) contains a similar analysis that includes several studies subsequent to the NRC report (BROW, HUMB, and LAMT). Wells' explicit criteria for studies to be analyzed excludes CHAN because it uses only current status of spouse smoking, but includes WU and Sandler et al. (1985), the latter of which has only a small number of lung cancer

cases. Wells' estimate of an average relative risk for lung cancer in nonsmoking females exposed to ETS is a little higher than the value obtained by the NRC, but both give 95% confidence intervals strictly above the value one. The location of the confidence interval in both references implies that the observed association between lung cancer incidence and exposure to ETS is statistically significant ($P< 0.05$ for a two-tailed test; $P<0.025$ for a test against the alternative of only a positive association). The NRC approach of estimating an overall relative risk from raw data in the studies, which appears in Blot and Fraumeni (1986) and Wald (1986) in addition to Wells, is extended in the next section to case control studies currently available (Table 2-1). Data on nonsmoking males married to a smoker are relatively sparse, so this report focuses on data for females where an association of passive smoking with lung cancer should be more detectable. The three cohort studies are treated separately here instead of including them in the overall analysis due to characteristic differences between case control and cohort studies.

Primary references for the 21 case control studies analyzed in this report are in Table 2-1. The Surgeon General's report (SG, 1986) contains particularly good summary reviews of the studies available at that time. The studies are selectively described or compared in several additional sources, e.g., NRC, 1986; IARC, 1987; Balter et al., 1986; Blot and Fraumeni, 1986; Correa, 1986; Eriksen et al., 1988; Kuller et al., 1986; Repace and Lowrey, 1985; Riboli, 1987; Samet, 1988a,b; Saracci and Riboli, 1989; Weiss, 1986; Wells, 1988b; Überla, 1987; Varela, 1987. Descriptions of the studies subsequent to the NRC report, two of which are unpublished dissertations (LAMW and VARE), are given in the Appendix. In addition to LAMW and VARE, the studies summarized there include BROW, GAO, GENG, HUMB, INOU, LAMT, SHIM, SVEN and WU.

2.2. THE NRC APPROACH TO AN OVERALL ESTIMATE OF RISK AND CONFIDENCE INTERVAL EXTENDED TO THE 21 CASE CONTROL STUDIES OF TABLE 2-1

The NRC (1986) and Wald (1986) use a common approach to estimate an overall relative risk across all studies using the method described by Yusuf et al. (1985). Blot and Fraumeni (1986) and Wells (1988b) achieve the same objective using the Mantel-Haenszel method (Mantel and Haenszel, 1959; Mantel, 1963), a standard approach for the combination of information from 2-by-2 contingency tables. As noted in Yusuf et al. (1985), however, the method described there is basically equivalent to the procedure of Mantel-Haenszel (M-H). The M-H method will be applied to the raw data for females available in the current case control studies (Table 2-5). The available data for males is also shown in Table 2-5. Studies have primarily been concerned with exposure to women in the home since nonsmoking males with wives who smoke are relatively uncommon. Additionally, a much smaller percentage of men than women stay at home during the day in some of the countries where the studies were conducted.

As in the NRC report, the raw data for the 2-by-2 classification (exposed or unexposed)-by-(case or control) will be used for each study. Several differences in the studies, however, need to be noted first. The meaning of "unexposed" differs between studies--a zero-exposure group is not always used for comparison with exposed groups. The unit of measure of exposure, e.g., cig./day or total years of exposure, varies across studies. Also, exposure environments may differ, e.g., smoking spouse at home, all smokers at home, exposure outside the home (such as at work). A few studies count former smokers as nonsmokers if they have abstained from tobacco usage for some specified time period, citing the commonly held view that the risk of lung cancer for an ex-smoker is approximately the same as for a never smoker of equivalent age within a few years after smoking is terminated. That belief has been brought into question

recently, however, in a reanalysis of the British doctors' data on smoking and lung cancer (Moolgavkar et al., 1989). It is readily apparent from Tables 2-5 that the case control studies are heterogeneous with respect to numerous characteristics aside from a variety of nationalities and cultures. (Statistical heterogeneity as in the sense of Breslow and Day (1980) is not intended here.)

Heterogeneity across studies is reflected in the proportion of the control group that is exposed to ETS. A plot of the proportions is shown in Figure 2- 1, which covers a range of about 43% to 84%, a two-fold difference, with the study BROW a low exception at 15%. The differences in proportions are more than can be accounted for by statistical variation, which would be the case if the referent populations (sampled control populations) were identical with respect to the meaning of "unexposed". The referent populations are not solely determined by the source of controls and their characteristics, such as being hospitalized or not, and whether subjects are alive or dead. Other characteristics play a role as well: study design, protocol, analysis, and interpretation of data; the definition of "exposure"; inclusion/exclusion of former smokers; source of information; potential confounding factors included in the matching and/or data analysis; and degree of confirmation of primary lung cancer in cases. Study differences in the observational meaning of "exposed" do not invalidate testing the hypothesis that exposure to ETS does not increase the risk of lung cancer, however, either for testing in a single study or for combining the test results across studies. This is because a test is based on the relative risk for each study, which is a within-study comparison between cases and controls. The overall (combined) test is valid because under the hypothesis tested the (true) relative risk equals one in each study, even if the referent populations differ. The statistical power to detect a small but meaningful increase in lung cancer risk from a single case control study is often fairly small, while the total power from assimilating test results may be considerably enhanced.

For estimating an overall relative risk, however, the study differences create some difficulty of interpretation. Judging from Figure 2-1, the true values of relative risk are not constant across studies. Qualitative differences are suggested by the variable sources of controls and the discrepant meanings of "unexposed" evident in Tables 2-1 to 2-4. What, then, is the interpretation of the parameter being estimated by the relative risk? Does it apply to a population of interest? It can be said with assurance that the parameter equals one if there is no risk of lung cancer associated with ETS exposure, is greater than one if there is a positive association of lung cancer risk with ETS, and is less than one if there is a negative association. The parameter will be referred to as the overall relative risk parameter (ORRP), and its estimate will continue to be called the overall relative risk estimate. Technically, it may be noted that the value of ORRP depends on the set of studies considered, so its (true) value may not be quite the same for this report and others. An estimate of the ORRP and an associated confidence interval are useful for hazard identification, i.e., in deciding if there is a lung cancer risk associated with ETS and in evaluating the strength of the evidence. It is not clear, however, to what extent an estimate of the ORRP may be useful for quantifying the degree of hazard (risk) for any real population of interest. This latter point is discussed further in Section 4.

The M-H estimate of relative risk (odds ratio) and its associated confidence interval are given in Table 2-5 for females of each case control study where the raw data are available. Our calculated values are shown in boldface type on the first line for each entry. The study author's estimate of the relative risk, most often the odds ratio, and the reported confidence interval are on the following line for comparison, as available. The M-H estimate of the overall relative risk parameter is 1.40 with 95% confidence interval (1.22,1.61), based on our calculated values for the 18 studies in Table 2-5 for which the raw data are available. The corresponding values in the NRC report for

females of ten case control studies and three cohort studies are 1.32 and (1.16, 1.51). (For reference, it is noted here that the NRC gives values of 1.62 and (0.99, 2.64) for males.) Wells (1988b) obtained an overall relative risk estimate of 1.50 with 95% confidence interval (1.3,1.8) for females from 14 case control studies, with some differences in the choice of studies compared to NRC and this report, as previously noted. The higher estimate may be attributable, at least in part, to Wells' exclusion of the CHAN study due to its use of only current smoking habits as a measure of exposure. The CHAN study was the first and probably most simplistic of the four Hong Kong studies. It produced the lowest estimated relative risk among the studies in Table 2-5, namely 0.75.

Aside from the difficulty of interpreting the overall relative risk estimate for inference on populations of interest, the method of calculating the confidence interval is contentious when there is significant between-study variability. The confidence interval produced by the M-H (or Yusuf) method of combining evidence across studies takes into account within-study variability, but not between-study variability. The "within" variability determines the confidence interval for a study by itself, while the "between" variability refers to variation of the relative risk across studies. Paul Meier (1987) has noted the potential for error if between-study variability is non-negligible but not taken into account. Meier's comments were made in the context of applying Yusuf's method to meta-analysis of clinical trials, but they are also relevant to the problem considered here.

A statistic referred to as "S" is included in Tables 2-5 and 2-6. It is the square-root of the M-H chi-squared statistic with the sign (+ or -) of (R -1), the odds ratio minus 1, attached. Equivalently, S is the estimated log-odds (ln(R)) divided by its estimated standard error. The estimator S is approximately normally distributed under the null hypothesis that the true relative risk for a study equals one (Woolf, 1955). The

values of Ps in Table 2-5 and Table 2-6 are the (one-tailed) significance levels of S for testing the null hypothesis against the alternative of elevated risk from ETS. Since S is standardized to account for sample size under the null hypothesis, its values are comparable between studies as evidence against the null hypothesis. The wide range of S values in Figure 2-2 suggests that between-study variability is probably too large to ignore, which casts some doubt on the actual size of the nominal 95% confidence intervals for the ORRP described above. This would need to be taken into consideration in any inference based on an overall confidence interval.

Confidence intervals have an equivalence in hypothesis testing. For example, an hypothesis that the ORRP equals a certain value, e.g., one, would be rejected with (two-sided) $P<0.05$ if a 95% confidence interval does not contain that value. If the level of the confidence interval is not 95% as claimed, however, then some adjustment would be in order that may have implications for tests of hypotheses inferred from the confidence interval. Since our interest is in a test of the hypothesis of no association between ETS exposure and lung cancer, however, a direct test can be made instead of relying on the confidence interval of the estimate of ORRP.

Under the hypothesis that the true relative risk value is one in each study, the between-study variability is zero, so the possible problem related to confidence intervals does not apply to a test of this hypothesis. The extended M-H chi-squared statistic for the test is significant at $P<0.001$, where the test applies to the raw data of studies in Table 2-5. The S statistics can be utilized to provide an alternative nonparametric test of the same hypothesis. The Wilcoxon sign-ranked test (Hollander and Wolfe, 1973) applied to the values of S in Table 2-5 is significant at $P=0.001$. The signed-rank test requires that the test statistic for each study is symmetrically distributed about zero under the null hypothesis. Since the statistic S is approximately normally distributed, that assumption should be satisfied within reason.

The two tests just applied are both statistically significant, but only the raw data have been examined. Several studies provide an adjusted statistical analysis, where "adjusted" refers to inclusion of potential confounding variables among the possible explanatory variables (along with exposure to ETS). An adjusted analysis is generally preferable to an analysis of the odds ratio from the raw data, even when the data are matched (Schlesselman, 1982, p. 190).

A second reason for examining the adjusted analyses is the large number of studies that appear not to be matched for passive smoking. Although most studies were originally matched on several variables, as shown in Table 2-1, many of the studies included issues in addition to ETS exposure and thus may be unmatched over the sample data for passive smoking. For example, several studies included active smokers which were then removed for analysis of passive smoking. Also, a study may not be matched due to the addition of supplementary data at a later time to increase the sample size or to collect different information, or just may be poorly matched due to study limitations or subject availability. A study originally designed for a purpose other than passive smoking, or designed for objectives in addition to passive smoking, could still be matched for analysis of lung cancer risk from exposure to ETS if smoking/nonsmoking is one of the variables used for matching, but no mention of that was found for any of the 18 studies considered here. Unfortunately, most studies do not state explicitly whether the data used to assess exposure to ETS alone are matched. If it appeared that a study may be unmatched for ETS, an entry of "No" is in Table 2-1. Using that rule, most of the studies are listed as unmatched for ETS, although the number could be overstated somewhat due to the general lack of specific information in several cases.

A combined test for an effect across studies with an adjusted statistical analysis is the topic of the next section.

2.3. META-ANALYSIS OF CASE CONTROL STUDIES THAT INCLUDE AN ADJUSTED STATISTICAL ANALYSIS

Table 2-1 identifies the studies in which an adjusted method of statistical analysis was used, generally logistic regression when reported. In most of the studies the relative risk and confidence interval are given for two or more levels of exposure, e.g., 1-20, 21-40, or 41+ cig./day smoked by the spouse, corresponding to 1 or less, 2 or less, and more than 2 packs/day. Outcomes of adjusted analyses are displayed in Table 2-6. The values of the relative risk, R, and the confidence intervals, are from the individual study reports except that reported 90% confidence intervals have been converted to 95% intervals. The table includes a comparison of unexposed with exposed when it is available in the study report. Some reports give results by exposure level, in which case the highest exposure level is used here since the power to detect an association of ETS and lung cancer should be highest there (other factors such as sample size aside). In some cases a report gives an estimated risk differential for some level of exposure, such as 20 cig./day smoked by the spouse, which is used in Table 2-6. The results recorded from adjusted statistical analyses are not directly comparable in most cases because of differences in what authors have reported. It is still valid, however, to test the hypothesis of interest, i. e., that lung cancer and ETS exposure are not associated, using all studies. The value of the statistic S in Table 2-6 was calculated for a study either from information on the estimated logistic regression function or from the confidence interval, in the latter case back-calculating to find the value of S that would produce the same confidence interval provided. Thus a value of S is being used that is consistent with an author's results in some sense, irregardless of how they were obtained. This approach provides some common ground for comparison.

In some studies where an extreme exposure level was used, there was more than one choice of what constitutes an extreme exposure case. The choices were generally due

to more than one exposure unit, e.g., cig./day, total years, etc. (see Table 2-4), or because more than one source of exposure to ETS is evaluated in a report, e.g., solely from spouse smoking in the home, from smoking by the spouse and others in the home, from one or more environments outside the home, etc., as indicated in Table 2-3. As a rule-of-thumb, preference was given exposure measured as cig./day in the home, generally due to spouse smoking alone. In none of the cases was the reported statistical outcome, for example the value of R, considered in the construction of Table 2-6.

The values of S for studies with an adjusted analysis are plotted in Figure 2-3. Of the significance values of S, Ps in Table 2-6 where Ps refers to the one-tailed significance level, five are 0.05 or less. If the hypothesis being tested is true, that the true relative risk value is one in each study, then five of the eleven tests are making a Type I error, i.e. are incorrectly finding a significant effect (at the 0.05 level). Assuming that the studies are independently conducted, which seems reasonable, the chance of observing five or more Type I errors in eleven independent studies is less than 0.001. If one chooses to exclude one of the studies for which Ps is 0.05 or less (for any reason), the corresponding probability for the remaining studies is 0.001 (figures are rounded). If two of the significant studies are excluded, leaving three of nine with Ps equal to 0.05 or less, the probability is still only 0.008. It is highly unlikely that so many significant test results would be observed if there is, in fact, no association between ETS exposure and lung cancer incidence. (Technical note: No multiple comparison adjustments are necessary for studies in which results for a single extreme exposure level are used because the choice of exposure level does not depend on statistical significance reported in the study. Test results reported at other exposure levels other than the one used are not relevant, and hence there is no implicit multiple comparisons to adjust for.)

The S statistics of Table 2-6 may be used in the Wilcoxon signed rank test, as conducted previously with the raw data, to provide another statistical test of the

hypothesis of interest. The test is significant with P=0.014. In this test the magnitude of the evidence from each study is a factor, in distinction to the dichotomization of studies as significant or not at the 0.05 level in the preceding calculation. Both statistical tests indicate that the cumulative evidence that lung cancer increases with ETS exposure would be very unlikely to occur by chance alone.

2.4. EVIDENCE OF TRENDS IN CASE CONTROL STUDIES WITH MORE THAN ONE EXPOSURE LEVEL

Data for studies that report relative risk by levels of exposure are given in Table 2-7, along with the results of statistical tests for trends when available. The relative risks are plotted by exposure and shown in Figure 2-4 (WU was inadvertently excluded from the figure, but the values for the plot are in Table 2-7). Some of the relative risks are estimated by adjusted statistical methods and some are not, as indicated in the table. Some observations are apparent from the plots. For example, the estimated relative risks never decrease from one exposure level to the next higher one in seven studies: AKIB, CORR, GAO, GENG, INOU, PERS, and TRIC; are monotonically decreasing (slightly) in one case: LEE; and are variable in the remaining five plots: GARF, HUMB, KOO, LAMT, and VARE. Trend tests depend on more than just the relative risk values shown in the plots on Figure 2-4, so one cannot make conclusions from the plots alone.

If relative risk (R) is not associated with ETS exposure, the observed values at all exposure values in a study should be equally likely to be greater or less than one since differences can be ascribed to chance variation instead of a causal mechanism, such as exposure to ETS or its correlates. Under the hypothesis of no association, the minimum R value at (positive) exposure levels in a study equals one or less with probability at least one-half. Only two studies out of the thirteen have an R value of

one or less in an exposed group (LEE and VARE), an event that would occur by chance with probability less than 0.012. If the number of exposure levels could be taken into account this figure would be smaller since there is more than one exposure level in each study, but the calculations are prohibitive because the R values within a study are correlated but unknown. It can be concluded, however, that the plots for trend are consistent with the previous statistical tests conducted on the case control studies.

2.5. BASIC ISSUES IN POTENTIAL BIAS FROM MISCLASSIFICATION IN CASE CONTROL STUDIES

Bias, and the potential source of it that has received the most attention, misclassification of subjects, is not limited to case control studies. Most of the attention in the literature, however, has been with respect to evaluation and interpretation of the case control studies, so the topic is reviewed here in that context.

2.5.1. Background

Estimation bias is due to study design, protocol, or method of analysis that *apriori* makes the expected outcome too large (positive bias) over too small (negative bias). Sample size and dispersion in the population sampled contribute to outcome variability, usually measured for an estimate by its standard error, but do not affect bias per se. If bias is zero, then a sufficient number of independent and identical repetitions of a study will assure that an estimate is arbitrarily close to the true value (on average). Alternatively, that same end can be achieved by making the sample size for the single study sufficiently large. Neither repeated sampling nor increasing the sample size affect bias; the estimate (on average) will simply becomes arbitrarily close to the unknown value of interest, i.e., the true relative risk plus the bias. In other words, sufficient data will overcome the statistical uncertainty due to sampling, but will

not affect bias because it is characterized by the methodology, not the observed data. In practice, each case control study has its own bias (possibly zero) and true relative risk, neither of which is observable. If bias is largely random over a set of studies, some averaging effect toward zero would be expected. If there is a consistent source of bias in studies, however, sometimes referred to as "systematic bias", then it cannot be expected to disappear as the number of studies available increases.

2.5.2. Sources of Bias

The NRC devoted considerable attention to the subject of misclassification before concluding that "while the epidemiologic studies show a consistent and, in total, a highly significant association between lung cancer and ETS exposure of nonsmokers, the excess might, in principle, possibly be explained by bias. However, detailed consideration of the nature and extent of the bias shows that given some reasonable assumptions, the bias would be insufficient to explain the whole effect. In fact, there are some types of bias that lead to underestimates of the effect. It must be concluded, therefore, that some, if not all, of the effect reported in spouse studies is causal" (NRC, 1986, p.242).

As reported recently by Saracci and Riboli (1989), two sources of bias may act to decrease the observed relative risk among nonsmoking women exposed to ETS by smoking spouses. First, this group of women is compared with other nonsmokers who are not "pure" subjects unexposed to ETS, as some of them may be exposed to other unrecorded sources of ETS, e.g., at work or in public places. Second, random misclassification of exposure tends to dilute any existing effect and its relative risk. Two other sources of bias would operate in the opposite direction of spuriously increasing the estimate of relative risk. First, it has been shown that smoking (nonsmoking) wives tend to be associated with smoking (nonsmoking) husbands. This would not bias the results

if there was not at the same time misreporting of the nonsmoker status. However, if some smoking women (or ex-smokers) are incorrectly reported as lifelong nonsmokers then a bias would be introduced. The size of this bias also depends on the relative risk among women misreported as nonsmokers. In addition, the magnitude of the bias depends on the proportion of smokers among males and females in the population under consideration. A further complication is introduced if the rate of misreporting of nonsmoking status is not the same for women exposed to spouses' ETS and women who are not exposed. The effect of differential misreporting has received very little attention, however, relative to the concern over inclusion of smokers or ex-smokers among the never smokers, and the misclassification of never smokers as exposed.

That subjects classified as unexposed are rarely purely unexposed is supported by data on cotinine measurements of body fluids indicating the ubiquity of ETS, which the NRC took into account in adjusting an overall relative risk for a "net" bias. Recent survey results of Cummings et al. (1989b) provide additional evidence of background exposure in never smokers. Detectable levels of cotinine were found in 132 of 162 (81%) of nonsmokers who reported no exposure in the four days preceding the interview. A mean urinary cotinine level of 8.8 ng/ml was found among nonsmokers. Although the study is based on self-selected volunteers, the authors note that the results are consistent with reports from other studies. Cummings and colleagues conclude that exposure to ETS is extremely prevalent, even among those not living with a smoker.

The NRC report's overall estimate of relative risk, i.e., estimate of the overall risk parameter (ORRP), places the increased risk of lung cancer from a smoking spouse at about 34%. An adjustment downward for possible misclassification of the never-smoker status brings the value to 25%. A further adjustment to make the risk relative to a purely unexposed subject, i.e., to take into account a background level of exposure, raises the increased risk to 42%. Consequently, the net adjustment for bias is upwards.

The reports of the Surgeon General (S.G., 1986) and IARC (1987) do not calculate an overall risk estimate and then adjust it for possible bias.

Wald et al. (1986) and the NRC committee followed a similar course in estimating overall risk and then adjusting for bias. For the same ten case control studies and three cohort studies (see Section 2.1), Wald and colleagues estimate the overall increased risk at 35%, with adjustments to 30% and then 53%, corresponding to the 25% and 42% figures above from the NRC report. In the more recent analysis of Wells (1988b) that includes 14 case control studies, the overall increased risk for females is 44%, which is then adjusted for bias in steps to 43% and then to 48%. Wells analyzes cohort studies separately for corroboration of the estimate from the case control studies. The methods of analysis and adjustment for possible bias by NRC and Wells are similar in approach but not identical in detail. Blot and Fraumeni (1986) calculated an increased risk for the same studies as the NRC, except with WU included but not BUFF or the cohort study by Gillis et al. (1984). The estimate of the overall risk parameter for females obtained by Blot and Fraumeni is 1.3, giving an increased risk of 30% compared to NRC's value of 34%. No adjustments were made for possible misclassification.

The diagnosis of lung cancer in cases may be a source of bias, e.g., a cancer that originated at another primary site and then spread to the lung may be incorrectly diagnosed as a primary cancer of the lung (Samet, 1988b). This misclassification tends to be random and therefore biases relative risk estimates toward unity (Copeland et al., 1977, as cited in Eriksen, 1988). As an example, Garfinkel et al. (1985) report that about 12% of lung cancer patients identified through hospital records were reclassified after histological review. Some studies addressed this issue by including only pathologically confirmed lung cancers or by considering histological cell type in their analyses (CORR, GARF, PERS, and others) (Eriksen, 1988).

Bias due to respondent by a proxy in place of the subject has also been raised as an issue by Mantel (1987b) and by Kilpatrick (1987), although they cite evidence from only two studies. Our review of VARE left us wondering about Figure No. 1 (Varela, 1985), wherein it appears that one aberrant point associated with surrogate respondents might be having an undue influence (a not uncommon occurrence in regression methods). As reported in Eriksen et al. (1988), respondent bias can be a source of negative or positive bias (Sackett, 1979), but in general the information provided by surrogates has been fairly comparable to that provided by the individuals themselves (Blot et al., 1985). The recent study by Cummings et al. (1989a) of the passive smoking histories of 380 never smokers further supports that conclusion. They report good agreement between subjects and surrogates on most exposure measures.

Vandenbroucke (1988) and Mantel (1987a) have questioned whether there may be a publication bias, studies with non-significant results being less likely to be published. Vandenbroucke constructed a quantitative approach but found that publication bias was only found compatible for the studies on men. Wells (1988a) reviewed the subject and concluded that it is unlikely that publication bias, i.e., the suppression of work with high standard errors by authors or reviewers, has any substantial effect on the relative risks that have been calculated from published reports for passive smoking for either men or women.

That misclassification might fully account for an observed increase risk of lung cancer from exposure to ETS remains a contention in some camps. Judging from the literature, the most ardent researcher is P. N. Lee (1984, 1986, 1987a, 1987b, 1988). His procedures and related quantitative assumptions, some of which lie outside the range considered likely in the NRC report, have evoked responses in the literature. For example, Wells (1988c) challenges some critical assumptions of Lee with evidence and data to the contrary. Doll and Peto (1986), in a letter responding to Lee, accuse him of

consistently selecting data and making choices otherwise that minimize the predicted risk of exposure to ETS. It is not our purpose here to fully review the arguments and cross-arguments on an issue that cannot be strictly proved or disproved, but requires reasoned judgment of the evidence. The recent report of an expert panel on passive smoking and lung cancer (Saracci, 1989) contains the following consensus opinion: "While for a few authors (Lee, 1988) bias can essentially account for the whole of the observed effect, it appears that this would demand the occurrence of a rather extreme combination of values of the relevant parameters. For instance, to wholly account for an observed relative risk of 1.35 requires as much as 10% of women reporting themselves as nonsmokers to be actually active smokers, with a relative risk of eight for lung cancer, and with an aggregation factor (odds ratio) of spouse smoking habits of 3.5. It seems thus unlikely that this type of bias could be the sole [underscored in source] explanation of the observed elevation in relative risk."

To give the reader some feeling for the sensitivity of the overall relative risk estimate to the misclassification of subjects, it was re-estimated from the raw data for females in the 18 studies in Table 2-5. The M-H approach was used, just as in Section 2.2, except with varied percentages of misclassification of subjects assumed. The percentage of misclassification among cases and among controls were addressed separately. For cases, a percentage X of the exposed group was reclassified as unexposed, after rounding to the nearest integer, and then the overall relative risk estimate was calculated. Values of X=1,2,3,...were tried until the significance level (p-value) of the M-H chi-squared statistic reached a value of 0.05. This was for a two-sided test so the corresponding p-value of a test against a one-sided alternative would be one-half that value (0.025). For cases, the two-sided p-value remained below 0.05 for values of X up to 7, i. e., up to 7 percent of the exposed cases in each study can be shifted (reclassified) as unexposed before the significance level exceeds 0.05. Among controls, 10 percent of

the unexposed group can be shifted to the exposed group before the p-value exceeds 0.05. If one could identify the current and/or ever-smokers in a study, then they would be removed from the analysis rather than reclassified. Statistical significance should be less sensitive to removing subjects than to reclassifying them, as done in this example. Reclassification would be appropriate for nonsmokers who are incorrectly classified according to exposure.

The main concerns raised in the literature regarding misclassification concerns cases. As discussed above, however, misclassifications could occur in cases or controls, and could occur differentially. The net reclassification (in the direction of reducing statistical significance) that could be distributed between controls and cases without exceeding the arbitrarily set significance level of 0.05 would likely fall between the 7 and 11 percent values found for cases and controls, respectively.

2.6. COHORT STUDIES: BACKGROUND

At this point we shift from review and discussion of the epidemiologic evidence in case control studies to the three cohort studies that have been conducted: Garfinkel et al. (1981); Gillis et al. (1984); and Hirayama (1981a, 1984); to be abbreviated as GARF(Coh), GILL(Coh), and HIRA(Coh), respectively. The use of "Coh" in parentheses is used to distinguish a cohort study from a case control study. The three studies are included in most of the references cited for summary descriptions and comparisons of case control studies in Section 2.1. The Surgeon General's report (SG, 1986) sketches the basic features of the cohort studies and the salient topics of controversy and discussion that appeared in the literature up to its time of preparation. The Scottish study, GILL(Coh), which observed only a very small number of lung cancer deaths (6 men and 8 women), is not discussed further in this report.

Unlike the case control studies, several of which have appeared since the NRC, IARC, and SG reports of 1986-87, the two major cohort studies, GARF(Coh) and HIRA(Coh), first appeared in 1981. Consequently, most of the issues regarding these two studies and their apparently discrepant results surfaced well before the three major reports were prepared. Critical scrutiny of the Hirayama study had already appeared and had been adequately addressed by Hirayama, as described in the SG and NRC reports. Judging from the roundtable discussion at the symposium "Medical Perspectives on Passive Smoking" (Lehnert, 1984), previous challenges to Hirayama's work regarding data analysis and other issues appear to have been resolved, aside perhaps from the omnipresent issue of potential misclassification. Without relinquishing the misclassification banner, even Mr. Lee offered a (qualified) concession to the strength of the statistical evidence in the Hirayama study: "It is ... clear in Dr. Hirayama's data that if one takes the age of the husband or wife into account and does the analysis correctly, there is a statistically significant association in lung cancer risk, but the significance is not nearly as marked as in the incorrect analysis."

Paradoxically, the study by Garfinkel and colleagues at the American Cancer Society (ACS) has undergone much less questioning and critical examination, although the problems experienced in conducting the study and the potential for error in the results has not gone unnoticed. The difference in outcomes in HIRA(Coh) and GARF(Coh) has been a source of concern to many, but to our knowledge no one has conducted a statistical review of GARF(Coh), as has been the case with HIRA(Coh), or compared the statistical methodology in the two studies. Those topics are addressed in the following section.

2.7. SOME COMPARATIVE ASPECTS OF TWO COHORT STUDIES: HIR(Coh) and GARF(Coh)

2.7.1. Overview

An increase in risk of lung cancer from ETS was observed in both cohort studies, with statistical significance ($P<0.05$), achieved in HIRA(Coh) but not in GARF(Coh). In the former study, the observed risk is nicely patterned, consistently increasing with higher levels of exposure from spouse smoking. Data from the American study estimate a higher risk at the lower of two exposure categories (spouse smokes <20 cig./day) than at the higher one (spouse smokes 20+ cig./day). Some researchers have interpreted this outcome as evidence that there is not a "dose-response" relationship in the American study, or more strongly, that the results demonstrate that there is no increased risk of lung cancer from ETS exposure. We find the statistical evidence inconclusive regarding a possible association between lung cancer incidence and ETS exposure, and consistent with what one would expect to observe in either the presence or absence of a true dose-response relationship. This conclusion follows from the 95% confidence intervals for the lung cancer mortality ratio at the low (<20 cig./day) and high (20+ cig./day) exposures, equal to (0.85, 1.89) and (0.77, 1.61) respectively. Technically these values could be adjusted for making multiple comparisons and for the use of a confidence interval corresponding to a two-sided test of significance rather than a one-sided test. The basic conclusion that the data are consistent with a wide range of possibilities, however, would remain. To illustrate this point with the confidence intervals given, the value 1.0 (corresponding to no increase in lung cancer mortality) is in both confidence intervals. Values corresponding to a substantial dose-response relationship are also in the intervals, e.g., 1.25 and 1.50 at the low and high exposures, respectively.

The American cohort study appears to contain more statistical uncertainty than the Japanese study, either due to real differences in risk associated with ETS, the presence of other factors that contribute to uncertainty in general, or both. Some of the general factors contributing to uncertainty in study data are related to sample size, variability in the population sampled, sample design and protocol, treatment of missing or incomplete data, accuracy and reliability of collecting and reporting data, and methods of statistical analysis. When the data produce a clear pattern such as HIRA(Coh), with a consistent upward trend across exposure categories and age groups that cannot be ascribed to chance alone, one has some assurance that the sources of variability ("noise") are sufficiently under control relative to the strength of an effect ("signal") in the data. This does not preclude possible bias, however, which is related to the tendency for estimates to be over- or understated on the average, and is not a component of variability per se.

In the following section the Japanese study (HIRA(Coh)) and the American study (GARF(Coh)) are reviewed, with an emphasis on the cultural differences in the populations sampled and the differences in study design, execution, and analysis of data that may help to compare outcomes of the two studies. In the final section, data comparisons are made for the two studies to evaluate if there is widespread differences across all age-exposure group combinations, or just specific ones.

2.7.2. Comparative Review and Discussion of Two Cohort Studies

HIR(Coh) is a census-population based study of adults aged 40 or above, begun in 1965 in 29 Health Center Districts in Japan. A total of 200 cases of lung cancer occurred among the 91,540 nonsmoking married women that were followed. In the whole study, 265,118 subjects were enrolled (122,261 males and 142,857 females) including unmarried women, accounting for 94.8% of the total census in the study area. Subjects

were tracked by establishing a record linkage system between the risk factor records and death certificates (Hirayama, 1983b, 1984). Blind interviews were conducted on the study subjects (NRC, 1986).

In the Japanese study, relative risks of 1.42, 1.58, and 1.91 were observed for nonsmoking wives with husbands who smoked 1-14, 15-19, and 20+ cigarettes per day, respectively. The corresponding value for women whose husbands were ex-smokers is 1.36, between the values for nonsmoking and light smoking husbands but closer to the latter (Hirayama, 1984). The observed increase in risk across the exposure categories, with ex-smokers classified as exposed between nonsmokers and the group for 1-14 cig./day, is statistically significant by the Mantel-Haenszel test (one-tailed $P<0.002$). Also, an increasing trend in risk related to husbands' smoking is reported when data are analyzed by age group (ten year periods), using either husbands' or wives' ages, or by occupational group or duration of exposure. No other characteristic of husbands or wives was found to be associated with the risk of lung cancer in nonsmoking women (Hirayama, 1983a).

The risk differential from exposure to ETS in the Japanese study was observed to decline with age, for all exposure groups. It is reported that although the risk relationship persists, there is an observable difference in the strength of the relationship for older and younger women. A clear-cut relationship was observed in younger women while the difference was rather small in older women (Lehnert, 1984). Some recent work showing an effect of age on lung cancer risk in active smokers may have some bearing on this issue. Moolgavkar et al. (1989) conclude that age likely influences lung cancer risk among smokers independently of duration of smoking. If this is true for passive smokers, then age of a nonsmoker exposed to ETS may be a factor aside from duration of exposure. Another possibility is suggested by Wells (1988b) who studied adult mortality from passive smoking. He comments that in passive smoking deaths we are

dealing with only the very most susceptible people. It may be that the more susceptible people constitute a relatively smaller proportion of the aged population at risk. This would follow if a subpopulation relatively more susceptible to lung cancer from exposure to ETS is also more susceptible to other health risks as well, reducing the rate of survival to old age. Future resarch may shed some light on this issue.

GARF(Coh), the American Cancer Society Prevention Study I, began in 1959 when a pyramidal structure of 68,000 volunteers in 25 states enrolled more than one million men and women for long-term follow-up. Volunteers were instructed to recruit people they knew well. Subject participation was fairly evenly divided across large cities, small cities and suburbs, small towns, and rural areas. Overall, about 3% of the population over the age of 45 in 1,121 counties was recruited. Enrollment included all family members of age 30 or above, provided at least one member of the household was at least 45. In the general plan of the study, the volunteers were to report annually on the status (alive or dead) of the subjects they enrolled, but some volunteers moved away or died in subsequent years, many of the subjects moved, and some volunteers did not follow instructions.

Each year, for six years, the volunteers were asked to report the vital status of the persons contacted (alive or dead). For subjects who had died, death certificates were obtained from state departments of health to determine whether death was due to lung cancer or not. Additionally, for the first six years, physicians who certified the cancer deaths were contacted and asked to supply information to verify the primary sites of the cancers. In the first six years, information was received confirming the primary site of cancer in 78% of the cases and microscopic confirmation was obtained in 69% of the cases. It was found that death certificates overstated the lung cancer rates by 11.8% (Garfinkel, 1981, 1984, 1985). The study was essentially terminated after six years, as originally planned in 1965, until it was decided to conduct a second follow-up in

1971-72. It is reported that the follow-up was successful for 98.4% of the subjects. It is also reported, however, that the follow-up was terminated because tracing became increasingly difficult due to death or movement of the volunteers and their substitutes (Garfinkel, 1985). Apparently death certificates did not continue to be followed-up by a medical report after the first six years. For lung cancer cases in all women, married or not, 203 out of a total of 564 (36%) reported by death certificates were accompanied by a medical report.

The American study is not conclusive regarding a possible association of lung cancer with ETS exposure. The ratio of observed to expected lung cancer deaths, referred to as the mortality ratio by Garfinkel (1981), is 1.27 and 1.10 for nonsmoking women with husbands who smoked <20 cig./day and 20+ cig./day, respectively. Neither value is reported to be statistically significant. When data from the Hirayama study are grouped according to the same exposure levels (<20 cig./day and 20+ cig./day), the observed relative risks are 1.45 and 1.91, with one-tailed p-values of 0.03 and 0.001 respectively (Hirayama, 1984).

As discussed in Section 2.7.1., apparent differences between outcomes of the two studies could be due to one or more sources: a real difference in risk in the populations studied; differences in the way the studies were designed, conducted, or interpreted; chance occurrence alone. There is some suggestive evidence for the first two alternatives. Subjects in the American study were followed for 12 years in comparison to 16 years in the Japanese study (Hirayama, 1984), so the proportion of subjects with lung cancer would be expected to be less in the American study, other factors aside. As reviewed in the Surgeon General's report (SG, 1986), the relatively high risks observed for nonsmokers whose husbands smoked led to speculation that Japanese women may report themselves as nonsmokers when they actually smoke (also see Lehnert, 1984), part of the general concern over misclassification in both case control and cohort studies

of ETS. Some reassurance of the validity of self-reported information from Japanese women, in general, came from the case control study of Akiba et al. (1986) (designated AKIB in this report). That study found strong concordance between smoking status reported by the women themselves and the reports from next of kin.

Hirayama has emphasized the importance of properly defining passive smoking, which he classifies as direct passive smoking, when the exposed subject is within a proximity of about 1-1.5 meters from the source of exposure, and indirect passive smoking, which applies to exposure from a greater distance (Hirayama, 1984; Lehnert, 1984). Direct passive smoking is of much greater concern than indirect passive smoking (Lehnert, 1984). Japanese wives may experience more direct passive smoking if they tend to be in closer proximity to their smoking husbands than American wives. Related factors that may contribute to a net increase in exposure of Japanese wives relative to their American counterparts include house sizes, the number of smokers per volume of air, climate and ventilation, proximity of nonsmoking spouse's sleeping area to spouse's smoking area, and the amount of time a nonsmoking spouse is in the home. Hirayama (1981b) notes additional differences between Japan and America that may influence exposure, such as a higher percentage of office workers among females in the United States than in Japan, a higher divorce rate in the United States, and the custom in Japan of smoking without first requesting consent.

There are also some differences in the methods of analyzing and interpreting data in the two cohort studies, as described in the next section.

2.7.3. Comparative Data Analysis of Two Cohort Studies

The measures of risk reported in HIRA(Coh) and GARF(Coh), the odds ratio and the mortality ratio, respectively, are not equivalent. Neither are the statistical methods for controlling for age the same. The method applied by Hirayama (Hirayama,

1984) is the Mantel-Haenszel procedure, commonly used to standardize for age and other factors that may have an influence. To control for age by this method, for example, study observations are grouped by time intervals. Comparisons between exposure groups are made at each time interval and then the results are combined across intervals to test for a difference between exposure groups (the extended M-H procedure). The analysis described by Garfinkel (1981), used in previous analyses of the same cohort study concerned with topics other than passive smoking (Hammond et al., 1976; Hammond, et al., 1975), is of a somewhat different nature. To adjust for age, each age group is weighted by a factor according to person-years with a smoking husband. Then the data are treated as quantal response data, i.e., there is one large data set with observations weighted by person-years. Expected deaths are based on the lung cancer rates by five-year age groups in women with nonsmoking husbands applied to the person-years of women with smoking husbands.

To adjust the analysis for several variables at once, in order to take into account potential confounding factors, the method previously applied to other data in the American study is used (Hammond et al., 1975, 1976). Matched groups are formed from the data, with the matching on age, race, highest educational status of husband or wife, residence, and whether or not husband is occupationally exposed to dust, fumes, or vapor (Garfinkel, 1981). The ratios of the number of adjusted lung cancer deaths in the low (<20 cig./day) and high (20+ cig./day) exposure categories to the control group, i.e., the nonsmoking women with nonsmoking husbands, are reported to be 1.37 and 1.04, neither of which is statistically signficant.

Based on the description in the two references to Hammond et al. cited by Garfinkel, under this method of adjusted analysis the data for subjects who cannot be fully matched would be discarded. This appears to have occurred in the analysis of passive smoking, judging from the estimates of the number of adjusted lung cancer

deaths in exposure groups (a range of 25 to 36, Table 5, Garfinkel, 1981). Provided we understand the procedure correctly, a downward adjustment would be expected due to the limitation of simultaneously matching on several variables. It would be of interest to compare the results obtained by a survival analysis approach that adjusts for covariates simultaneously while using all the data. Such an approach would also have some limitations, but it is likely that the power to detect an effect, if there is one, would be improved.

Using data for the American study that includes age at time of death, duration on study, and whether death was due to lung cancer or another cause (supplied by L. Garfinkel), the Mantel- Haenszel method was applied with age and duration on study controlled. The results were not close to statistical significance.

To see if we could gain further insight into the outcome in the American study, the descriptive data from GARF(Coh) corresponding to the age groups and exposure classifications of data published for HIRA(Coh) (Hirayama, 1984, Table 1) were placed side-by-side for visual comparison (Table 2-8). Relative to the general pattern of response in the Japanese study, the American data appear to be at greatest variance from what might be expected in the two subgroups at highest exposure (20+ cig./day) with age classifications 40-49 and 50-59. Further review of those data for completeness, possible sources of bias, or unanticipated anomalies may be useful.

2.8. FROM HAZARD IDENTIFICATION TO RISK ASSESSMENT

In this chapter, the epidemiologic evidence of an *association* of ETS exposure and lung cancer incidence has been considered. The question addressed has been simply: Is there evidence of increased lung cancers among persons chronically exposed to ETS after adjusting for sampling variability, i.e., beyond the laws of chance? Chance

occurrence alone is extremely unlikely, based on the consistent outcomes of the several analytical approaches described in this chapter.

Whether ETS exposure *causes* an increase in lung cancer, only *contributes* to it, or acts as a *surrogate* for another cause(s) correlated with ETS exposure cannot be ascertained from data analysis alone. Most studies attempted to account for other factors that may contribute to lung carcinogenesis or otherwise confound the study interpretation. Particular attention was given to adjusted analyses and trends in Sections 2.3 and 2.4 above. If ETS is not implicated as a causal factor at all, the "joker" (to quote Hirayama (Lehnert, 1986)) is elusive indeed.

If ETS is a risk factor for lung cancer, to what extent can exposure levels be quantitatively related to risk estimates, i.e., can a meaningful quantitative dose-response relationship be determined? Published risk assessments of ETS have largely relied on extrapolation of the overall relative risk estimate to a population of interest, an approach for which some reservations are implied by our Section 2.2, or extrapolation to an estimated dose-response relationship for active smokers based on a presumption of equivalence of passive smoking at some specified ETS exposure level to active smoking of some number of cigarettes, i.e., a "cigarette equivalence" for ETS exposure. That approach may depend heavily on assumptions related to the biokinetics of active and passive smoking, and the distribution of carcinogens between the particulate and vapor phases in mainstream smoke and sidestream smoke. That topic is addressed in the next chapter, followed by a review and discussion of dose surrogates and risk assessments for passive smoking in Chapter 4.

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TABLE 2-1. CASE-CONTROL STUDIES – CHARACTERISTICS

Study	Location	Matched variables	Final sample matched for ETS?	Adjusted statistical analysis?
AKIB (Akiba et al. 1986)	Japan (Hiroshima, Nagasaki)	Age, sex, residence, RERF participant	Yes	No
BROW[1] (Brownson et al., 1987)	USA (Colorado)	Age, sex	No[2]	Yes
BUFF (Buffler et al., 1984)	USA (Texas)	Age, sex	No[2]	No
CHAN (Chan and Fung, 1982)	Hong Kong	Matched but variables unspecified	No[2]	No
CORR[3] (Correa et al., 1983)	USA (Louisiana)	Age (±5), sex, race	No[2]	No
GAO (Gao et al., 1987)	China (Shanghai)	Age (±5)	No[2]	Yes
GARF (Garfinkel et al., 1985)	USA	Age (±5)	Yes	Yes
GENG (Geng et al., 1986)	China (Tianjin)	Age (±2), sex, race, marital status	No[2]	No
HUMB (Humble et al, 1987)	USA (New Mexico)	Age (±10), sex ethnicity	No[2]	Yes
INOU (Inoue and Miraijama, 1988)	Japan (Kanagawa, Miura)	Age, year of death (±2.5), district	No[2]	Yes
KABA (Kabat and Wynder, 1984)	USA (New York)	Age (±5), sex, race, hospital	Yes	No
KOO (Koo et al., 1987)	Hong Kong	Age (±5), residence, housing	No[2]	Yes

TABLE 2-1. Continued

Study	Location	Matched variables	Final study matched for ETS?	Includes an adjusted statistical analysis?
LAMT (Lam et al., 1987)	Hong Kong	Age (± 5), residence	No[2]	No
LAMW (Lam, 1985)	Hong Kong	Age, socioeconomic status, residence[5]	No[2]	Yes
LEE (Lee et al., 1986)	England	Age, sex, hospital location, time of interview	No[2,4]	No
PERS (Pershagen et al., 1987)	Sweden	Age (± 1), sex	Yes	Yes
SHIM (Shimizu et al., 1988)	Japan (Nagoya)	Age (± 1), hospital, admission date	Yes	Yes
SVEN (Svensson et al., 1988)	Sweden (Stockholm)	Age	No[2]	Yes
TRIC (Trichopoulos et al., 1981)	Greece (Athens)	Age, socio-economic status[6]	No[2]	No
VARE (Varela, 1987)	USA (New York)	Age, sex, county, smoking history	Yes	Yes
WU	USA (Los Angeles)	Age (± 5), sex, race	No[2]	Yes

[1]Adenocarcinoma only.
[2]Not matched on smoking status (smoker/non-smoker).
[3]Bronchioalveolar cancer excluded.
[4]Ongoing study modified for passive smoking with follow-up.
[5]"Similar" in age, SES, and residence.
[6]"Similar" in age and SES.

TABLE 2-2. CASE-CONTROL STUDIES – CHARACTERISTICS

Study	Percent Proxy Response[1]		Female[2] Age		Source of Controls	Number Female Controls	Percent Female Controls "Exposed"[3]
	Ca	Co	Ca	Co			
AKIB	90	88	70.2 35-95	• •	Atomic bomb survivors	270	70
BROW	69	39	66.3	68.2	Cancer cases[4]	47	15[5]
BUFF	82	76	30-79	30-79	Cancer cases[6]	196	84[7]
CHAN	•	•	39-70+	39-79+	Orthopaedic patients	139	47
CORR	•	•	•	•	Hospital patients[8]	133	46
GAO	0	•	35-69	35-69	General population	375	74
GARF	•	•	≥40	≥40	Cancer cases[9]	402	61
GENG	•	•	≤65	≤65	•	93	44
HUMB	•	•	≤85	≤85	General population	162	56
INOU	100	100	•	•	Cerebrovascular disease (deaths)	64	•
KABA	•	•	61.6	53.9	Patients[10]	25	60
KOO	•	•	•	•	"Healthy"[11]	136	49
LAMT	•	•	•	•	"Healthy"[12]	335	45
LAMW	•	•	67.5	66	Hospitalized orthopedic patients	144	44
LEE	38[13]	38	35-74	35-74	Patients[14]	66	68
PERS	•[15]	•	•[16]	•	•[17]	347	43

TABLE 2-2. Continued

Study	Percent Proxy Response[1]		Female Age[2]		Source of Controls	Number Female Controls	Percent Female Controls "Exposed"[3]
	Ca	Co	Ca	Co			
SHIM	•	•	59 35-81	58 35-81	Patients[18]	•	•
SVEN	0	0	66.3		General population	174	66
TRIC	•	•	62.8	62.3	Hospitalized orthopedic patients	190	43
VARE	33[19]	33[19]	67.1[19]	68.1[19]	New York State Dept. of Motor Vehicles	218[20]	•
WU	•	•	<76	<76	Neighborhood[12]	52	63

[1]"ca" and "co" stand for "cases" and "controls", respectively.
[2]Single values are the average or median. Paired values are the range.
[3]Definition of "exposed" differs between studies. See Table 2-4 and Table 2-5.
[4]Persons with cancers of bone marrow or colon in Colorado Control Cancer Registry.
[5]"Exposed" if husband smoked.
[6]Population-based and decedent comparison subjects selected from state and federal records.
[7]"Unexposed" includes up to 32 total years of living with a household member who smoked.
[8]Assorted ailments.
[9]Colo-rectal cancer.
[10]Diseases not related to tobacco.
[11]Selected from a healthy population.
[12]Living in neighborhood of matched case.
[13]Applies only to the 143 patients in the follow-up study.
[14]Excluding lung cancer, chronic bronchitis, ischemic heart disease, and stroke.
[15]No overall percentages given.
[16]Two control groups: 15-65 and 35-85 for both cases and controls in groups 1 and 2 respectively.
[17]Two controls groups were randomly chosen from the cohort under study.
[18]Patients in the same or adjacent wards with other diseases.
[19]Includes males and females.
[20]Includes 69 former smokers.

TABLE 2-3. CASE-CONTROL STUDIES – ETS SOURCES

Study	Adulthood				Childhood Exposure From Mother/Father
	Spouse(s)		Others at Home	Away from Home	
	1	>1			
AKIB	X				X
BROW	X		X	X	
BUFF			X		
CHAN[1]	X				
CORR		X			X
GAO		X	X	X	X
GARF		X	X	X	
GENG	X		X[2]	X	
HUMB		X			
INOU	X				
KABA	X		X	X	
KOO	X		X		
LAMT	X				
LAMW	X		X	X	
LEE		X		X[3]	
PERS	X				X
SHIM	X		X	X	
SVEN	X		X	X	X
TRIC		X			
VARE		X	X	X[4]	
WU		X	X	X	X

[1]As reported in Chan, 1982. In Chan, 1979, exposure is described as at home or at work.
[2]Exposure to mother's or father's smoking is presumed to mean in adulthood.
[3]Separate for workplace, travel, leisure.
[4]Separate for workplace and social circumstances.

TABLE 2-4. MEASURES OF ETS EXPOSURE
AND EXPOSURE TO POTENTIALLY RELATED SUBSTANCES

Study	ETS Exposure Measures				Related Exposures	
	Cigarettes/ Day	Total Years	Total Cigarettes	Other	Cooking/ Heating	Work/ Environ.
AKIB	X					
BROW				hrs/day		X
BUFF		X				X
CHAN				X[1]	X	
CORR				pack-yrs		
GAO		X			X	X
GARF	X[2]			hrs/day		
GENG	X	X				
HUMB	X	X				
INOU	X[3]					
KABA				no units		X
KOO	X	X		X[4]		
LAMT	X[5]					
LAMW				no units		
LEE				X[6]		X
PERS				no units		X
SHIM	X				X	X
SVEN				X[7]		
TRIC	X[8]		X			
VARE	X	X	X	person-yrs		

TABLE 2-4. Continued

Study	Exposure Measures: Cigarettes/ Day	Total Years	Total Cigarettes	Other	Related Exposures: Cooking/ Heating	Work/ Environ.
WU				X[9]	X	X

[1]Exposed/unexposed determined from a single question, "Are you exposed to the tobacco smoke of others at home or at work?" (Lam T.H. et al., 1987).
[2]Cig/day smoked by husband at home.
[3]Smoker at home defined as $\geq$5 cig/day.
[4]Others include total hours of exposure and mean hrs/day.
[5]A woman was considered exposed to her husband's smoke if they had lived together continuously for at least one year.
[6]Exposure designated as 0 (unexposed), 1, 2, 3.
[7]Exposure is "yes" or "no" for each source.
[8]Exposed within last 5 years.
[9]Exposed if husband smoked.

TABLE 2-5. CASE-CONTROL STUDIES – "UNEXPOSED" vs. "EXPOSED" FEMALES FROM RAW DATA

Study	Exposure	No. Cases	No. Controls	R^1	C.I.[1]	S^1	P_S^1
AKIB							
Female	0	21	82	**1.52**	**(0.88, 2.64)**	**1.48**	**0.07**
(Cig/day)	≥1	73	188	1.5	(1.0, 2.5)[2]		
Male	0	16	101				
(Cig/day)	≥1	3	19	1.8	(0.5, 5.6)		
BROW[3]							
Female	unexposed	15	40	**1.52**	**(0.39, 5.99)**	**0.61**	**0.27**
	exposed[4]	4	7	1.5	•		
Male	0–3	2	11				
(Hrs/day)	≥4	2	8	1.38	•		
BUFF							
Female	0–32	8	32	**0.81**	**(0.34, 1.90)**	**-0.49**	**0.69**
(Tot. yrs)	≥33	33	164	0.8	(0.3, 1.8)		
Male	0–32	6	34				
(Tot. yrs)	≥33	5	56	0.5	(0.2, 1.7)		
CHAN							
Female	unexposed	50	73	**0.75**	**(0.43, 1.30)**	**-1.02**	**0.85**
	exposed[5]	34	66	0.8	(0.4, 1.3)		
CORR							
Female[6]	0	8	72	**2.07**	**(0.82, 5.20)**	**1.52**	**0.06**
(Pack-yrs)	≥1	14	61	2.07	(0.8, 5.0)		
Male	0	6	154				
(Pack-yrs)	≥1	2	2.6	2.0	•		

TABLE 2-5. Continued

Study	Exposure	No. Cases	No. Controls	R[1]	C.I.[1]	S[1]	P_S^1
GAO							
Female	0-19	57	99	**1.19**	**(0.82, 1.73)**	**0.91**	**0.18**
(Tot. yrs)	≥20	189	276	•	•		
GARF							
Female	0	44	157	**1.31**	**(0.87, 1.98)**	**1.29**	**0.10**
(Cig/day)	≥1[7]	90	245	1.31	(0.99, 1.73)		
GENG							
Female	0	20	52	**2.16**	**(1.09, 4.28)**	**2.19**	**0.01**
(Cig/day)	≥1	34	41	2.16	(1.93, 4.53)		
HUMB[8]							
Female	0	5	71	**2.34**	**(0.83, 6.61)**	**1.57**	**0.06**
(Cig/day)	≥1	15	91	1.8	(0.6, 5.4)		
INOU							
Female	0-4[9]	•	•				
(Cig/day)	≥5	18	30	2.25	(0.91, 7.10)		
KABA		37	74				
Female	unexposed	11	10	**0.79**	**(0.25, 2.48)**	**-0.41**	**0.66**
	exposed[10]	13	15	•	•		
KOO							
Female	0	35	70	**1.55**	**(0.90, 2.67)**	**1.56**	**0.06**
(Cig/day)	exposed[11]	115	66	1.55	(0.94, 3.08)		

why was this used ≠ not 1.86 - see p. A-9

should this be (A-4) 1.05

why did you calculate 90% C.I.?

how was this calculated if exp status 2 levels, & 37 cases of which [illegible] status [illegible]

what is discrepancy - appendix says 37 cases

TABLE 2-5. Continued

Study	Exposure	No. Cases	No. Controls	R[1]	C.I.[1]	S[1]	P_S^1
LAMT							
Female	0	84	183	1.65	**(1.16, 2.35)**	2.77	0.003
(Cig/day)	≥1	115	152	1.65	(1.16, 2.35)		
LAMW							
Female	unexposed	23	80	**2.01**	**(1.09, 3.71)**	2.22	0.01
	exposed[11]	37	64	2.01	•		
LEE							
Female	unexposed[12]	10	21	**1.03**	**(0.41 2.56)**	0.06	0.48
	exposed[13]	22	45	1.00[14]	(0.37, 2.71)[14]		
PERS							
Female	unexposed[15]	34	197	**1.28**[14]	**(0.76, 2.15)**	0.91	0.18
	exposed[16]	33	150	1.28[14]	(0.75, 2.15)		
SVEN							
Female	unexposed	10	60	**1.26**	**(0.57, 2.81)**	0.57	0.28
	exposed[16]	24	114	•	•		
TRIC							
Female	0	24	109	**2.13**	**(1.19, 3.81)**	2.53	0.0063
(Cig/day)	≥1	38	81	•	•		
WU							
Female[17]	unexposed	9	19	**1.12**	**(0.46, 3.24)**	0.39	0.35
	exposed[4]	19	33	•	•		

Footnotes for Table 2.5.

[1]Values of R, C.I., S, and P_S on the first row of an entry (boldface) are our calculations for Mantel-Haenszel odds ratio. Values in the second row are from the study. S is the square root of the Mantel-Haenszel statistic with sign of (−) if $R<1$ and (+) if $R>1$. P_S is one-tailed from normal tables, and equals one-half the corresponding two-sided P value for the M-H chi-squared statistic. Confidence intervals are 95% unless noted otherwise.

[2]90% C.I.

[3]Data communicated from R.C. Brownson.

[4]Exposed if husband smoked.

[5]Exposure based on single question, "Are you exposed to the tobacco smoke of others at home or at work?" (Lam, T.H., et al., 1987a).

[6]Data partially from Table 12-4, NRC (1986).

[7]Cigar or pipe smoking by husband while at home is included in category of ≥ 1 cig/day.

[8]Data communicated from C.G. Humble.

[9]Husbands who smoke less than 5 cig/day are presumed not to smoke at home.

[10]Based on spouse's current or past smoking habits.

[11]Exposed if husband ever smoked in presence of spouse.

[12]Only the controls in the follow-up study.

[13]Exposed if husband ever smoked during marriage.

[14]Standardized for age.

[15]Data for controls from Saracci and Riboli (1989).

[16]No measure of exposure given.

[17]Data from Blot and Fraumeni (1986).

TABLE 2-6. CASE CONTROL STUDIES – "UNEXPOSED" vs. "EXPOSED" FEMALES FROM ADJUSTED STATISTICAL ANALYSES

Study	Exposure	R	95% C.I.	S	P_S
BROW	≤3 vs. ≥4 (hrs/day)	1.68	(0.39, 2.97)	1.78	0.04
GAO	0–19 vs. ≥40 (yrs. with smoking husband)	1.7	(1.0, 2.9)	1.95	0.03
GARF	0 vs. 20 (cig/day)	1.70	(0.98, 2.94)	1.90	0.03
HUMB	0 vs. ≥21 (cig/day)	1.2	(0.26, 5.5)	0.23	0.41
INOU	≤4 vs. ≥20 (cig/day)	3.09	(1.04, 11.81)	1.65	0.05
KOO	0 vs. ≥21 (cig/day)	1.19	(0.46, 3.03)	0.36	0.36
LAMW[3]	Exposed by husband	2.64	•		•
LEE[5]	Exposed by husband	1.00	(0.37, 2.71)	0.00	0.50
PERS[1]	0 vs. ≥16 (cig/day)	2.4	(0.6, 8.7)	1.33	0.09
SHIM[2]	Exposed by husband	1.1	•	•	•
SVEN	Exposed in both childhood and adulthood vs. exposed in neither	1.9	(0.2, 3.7)	1.89	0.03
VARE[4]	0 vs. 20 (cig/day)	0.94	(0.76, 1.17)	−0.54	0.70
WU	Exposed by husband	1.2	(0.6, 2.5)	0.49	0.31

[1]See footnotes 15–17 of Table 2–2.

[2]Higher R values associated with adult exposure to smoking by mother or by father's husband. Insufficient information to calculate the S statistic.

[3]No units of exposure. R = 2.64 with p = 0.02, and R = 1.61 with P = 0.19, for peripheral and central lung adenocarcinoma, respectively.

[4]From Table 4 of Varela, 1987.

[5]See footnotes 12-14 of Table 2-5. Study is included with adjusted statistical analyses in this table since analysis was standardized for age.

TABLE 2-7. CASE-CONTROL STUDIES – EXPOSURE-RESPONSE TRENDS FOR FEMALES

Study	Exposure	R	C.I.[1]	P-Trend	Analysis	
					Unadjusted	Adjusted
AKIB	0	1.0		0.06	X	
(Cig/day)	1-19	1.3	(0.7, 2.3)[2]			
	20-29	1.5	(0.8, 2.8)[2]			
	≥30	2.1	(0.7, 2.5)[2]			
CORR	0	1.0		•	X	
(Pack-yrs)	1-40	1.18	•			
	≥41	3.52	•			
GAO	0-19	1.0		•		X
(Tot. yrs)[3]	20-29	1.1	(0.7, 1.8)			
	30-39	1.3	(0.8, 2.1)			
	≥40	1.7	(1.0, 2.9)			
GARF	0	1.0		<0.025	X	
(Cig/day)	1-9	1.15	(0.8, 1.6)			
	10-19	1.08	(0.8, 1.5)			
	≥20	2.11	(1.1, 4.0)			
GENG	0	1.0		•	X	
(Cig/day)	1-9	1.40	(1.1, 1.8)			
	10-19	1.97	(1.4, 2.7)			
	≥20	2.76	(1.9, 4.1)			
HUMB	0	1.0		•	X	
	1-20	1.8	(0.6, 5.6)[2]			
	≥21	1.2	(0.3, 5.2)[2]			
INOU	0-4	1.0		<0.05		X
(Cig/day)	5-19	2.58	(0.4, 5.7)[2]			
	≥20	3.09	(1.0, 11.8)[2]			
KOO	0	1.0		•		X
(Cig/day)[4]	1-10	2.33	(0.9, 5.9)			
	11-20	1.74	(0.8, 3.8)			
	≥21	1.19	(0.5, 3.0)			

TABLE 2-7. Continued

Study	Exposure	R	C.I.[1]	P-Trend	Analysis: Unadjusted	Analysis: Adjusted
LAMT[5]	0	1.0		<0.01	X	
(Cig/day)	1-10	2.18	(1.14, 4.15)			
	11-20	1.85	(1.19, 2.87)			
	≥21	2.07	(1.07, 4.03)			
LEE[6]	0	1.0		•	X[6]	
	Low	0.92	•			
	High	0.81	•			
PERS[7]	0	1.0		•	X[8]	
(Cig/day)	1-15	1.8	(0.6, 5.3)			
	≥16	6.4	(1.1, 34.7)			
TRIC[9]	0	1.0		•	X	
(Cig/day)	1-20	1.95	•			
	≥21	2.55	•			
VARE[10]	0	1.0		•		X
(Cig/day)	1-20	0.79	(0.6, 1.1)			
	21-40	0.91	(0.6, 1.3)			
	41-60	1.23	(0.6, 2.4)			
	61-80	0.42	(0.1, 2.3)			
	80+	2.86	(0.3, 27.7)			
WU[11]	0	1.0		•		X
(Yrs. exposed	1-30	1.2	•			
as adult)	≥31	2.0	•			

[1]Confidence intervals are 95% unless noted otherwise.
[2]90% C.I.
[3]Years lived with a smoking husband.
[4]Cig/day smoked by husband.
[5]All histologies.
[6]Exposure at home only. Standardized for age, spouse smoking, and whether marriage was ongoing or ended.
[7]Small cell carcinoma only. Observed risk was lower for other histologies combined.
[8]Standardized for age.
[9]Data from Trichopoulos et al. (1983).
[10]From Table 2 of Varela (1987) for spouse smoking, presumably including males.
[11]Adenocarcinomas only.

TABLE 2-8. TWO COHORT STUDIES – FEMALE LUNG CANCER DATA FOR SIMILAR AGE AND EXPOSURE GROUPS[1]

Age[3]	Study[4]	Husband's Smoking Habit[2]		
		Nonsmoker	1-19	20+
40-49	G	9/23,743 (3.8)	6/11,791 (5.1)	12/26,918 (4.5)
	H	4/6,229 (6.4)	14/13,779 (10.2)	16/10,764 (14.9)
50-59	G	31/25,108 (12.3)	25/13,528 (18.4)	21/24,184 (8.7)
	H	10/7,791 (12.8)	28/13,720 (20.4)	24/9,820 (24.4)
60-69	G	23/15,138 (15.2)	16/6,884 (23.2)	20/7,299 (27.4)
	H	18/7,120 (25.3)	37/9,756 (37.9)	23/4,651 (49.4)

[1] Entries are (number of lung cancer deaths)/(number at risk). Values ($x10^4$) are in parentheses. Data for age 70-79 are omitted because of small sample sizes and small number of lung cancers observed. Data for "G" were supplied by L. Garfinkel. Data for "H" are in Hirayama (1984).

[2] Cigarettes/day.

[3] Women's age for G; Husband's age for H.

[4] G: GARF (Coh) H: HIRA (Coh).

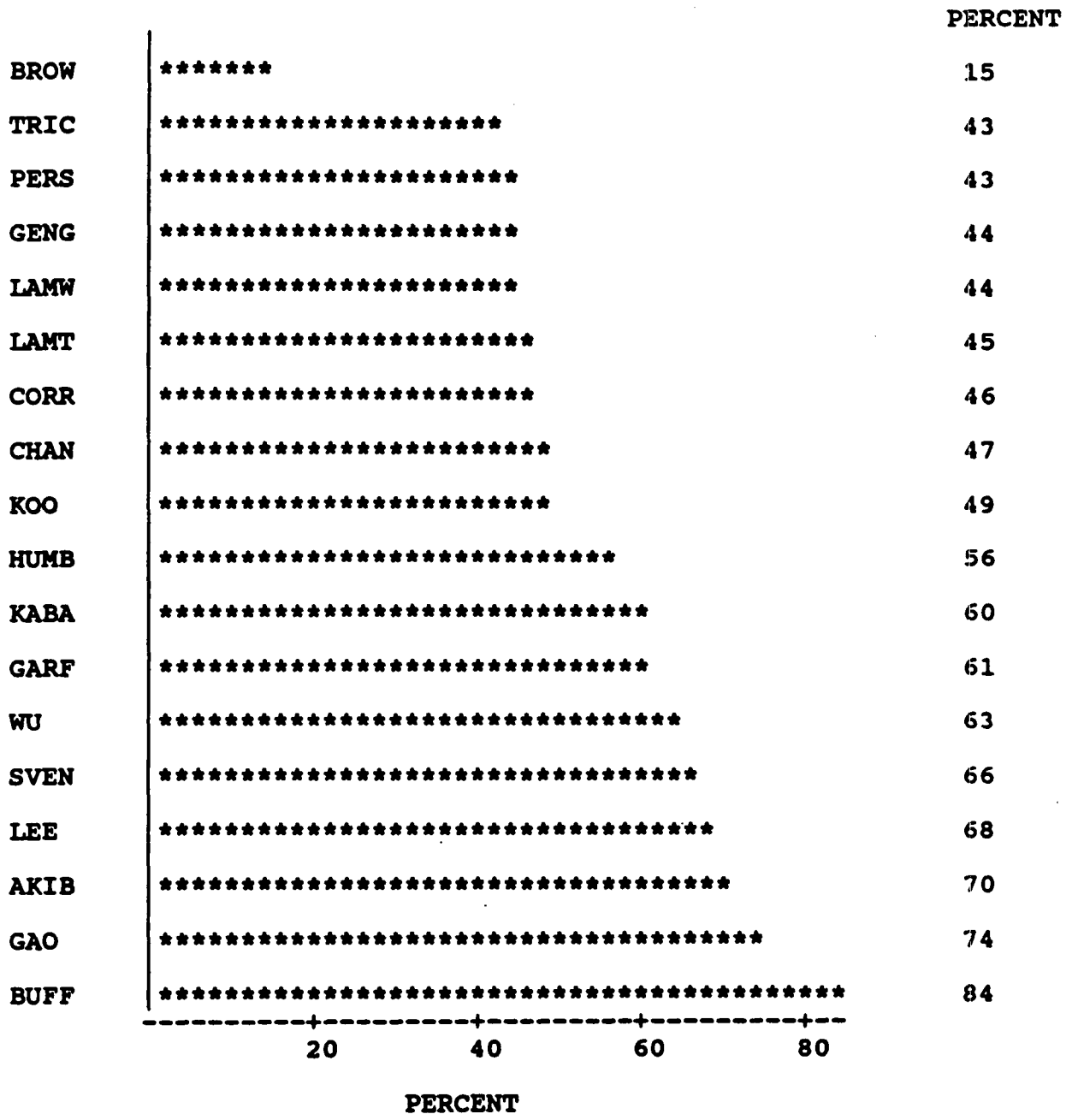


Figure 2-1. Percentage of controls exposed to ETS by study.

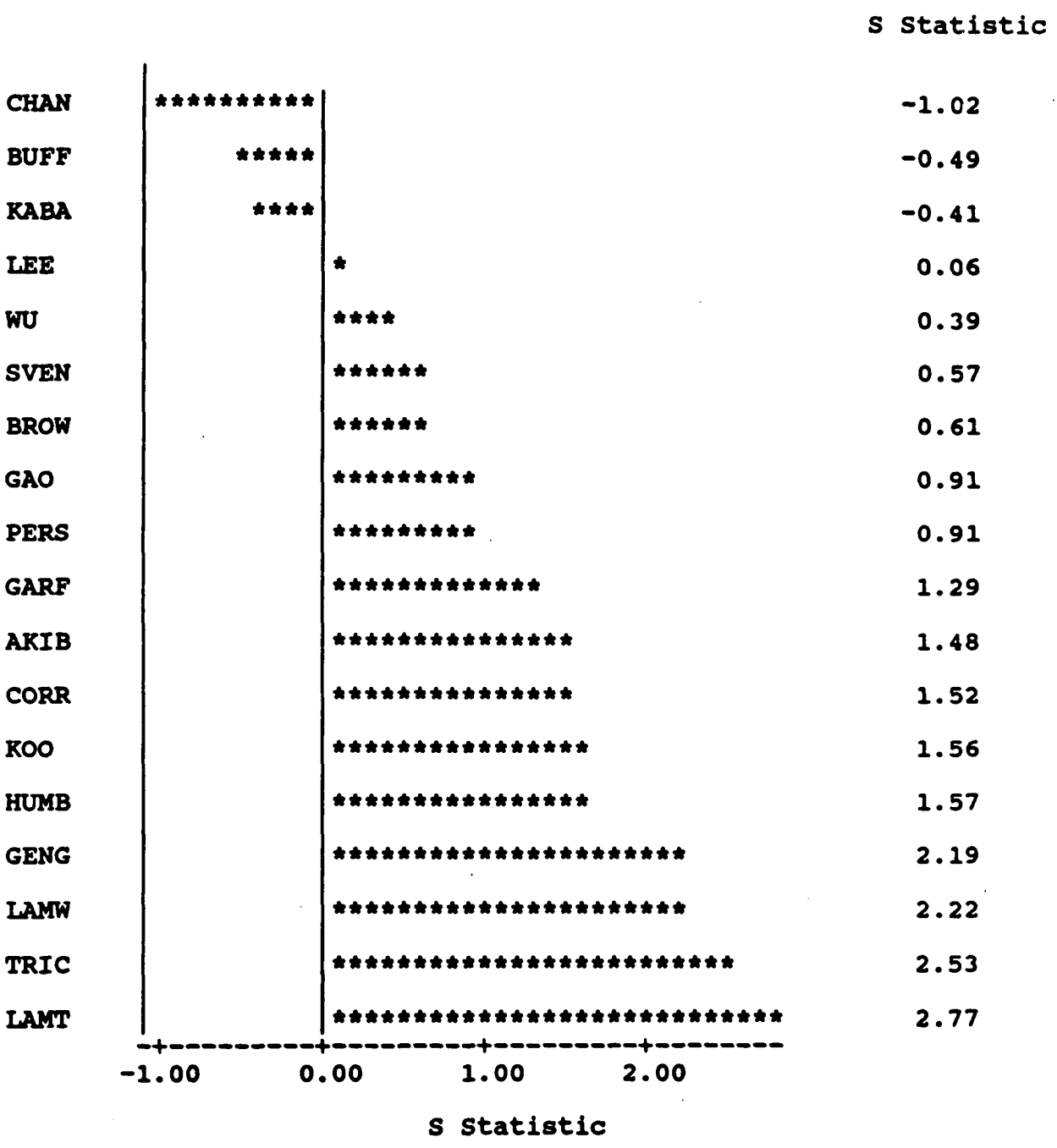


Figure 2-2. Ordered values of the S statistic from raw data of studies in Table 2-5.

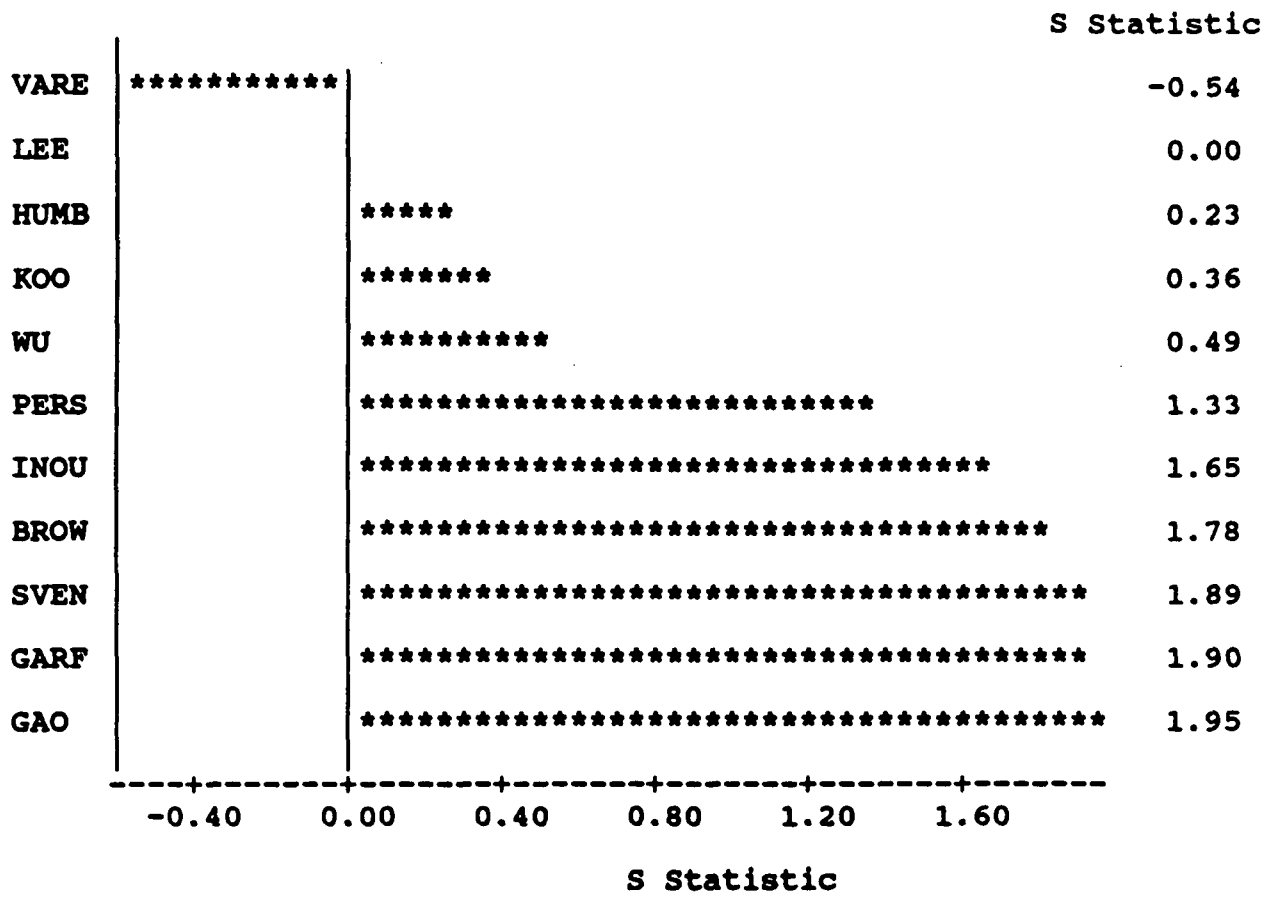


Figure 2-3. Ordered values of the S statistic from adjusted analyses of studies in Table 2-6.

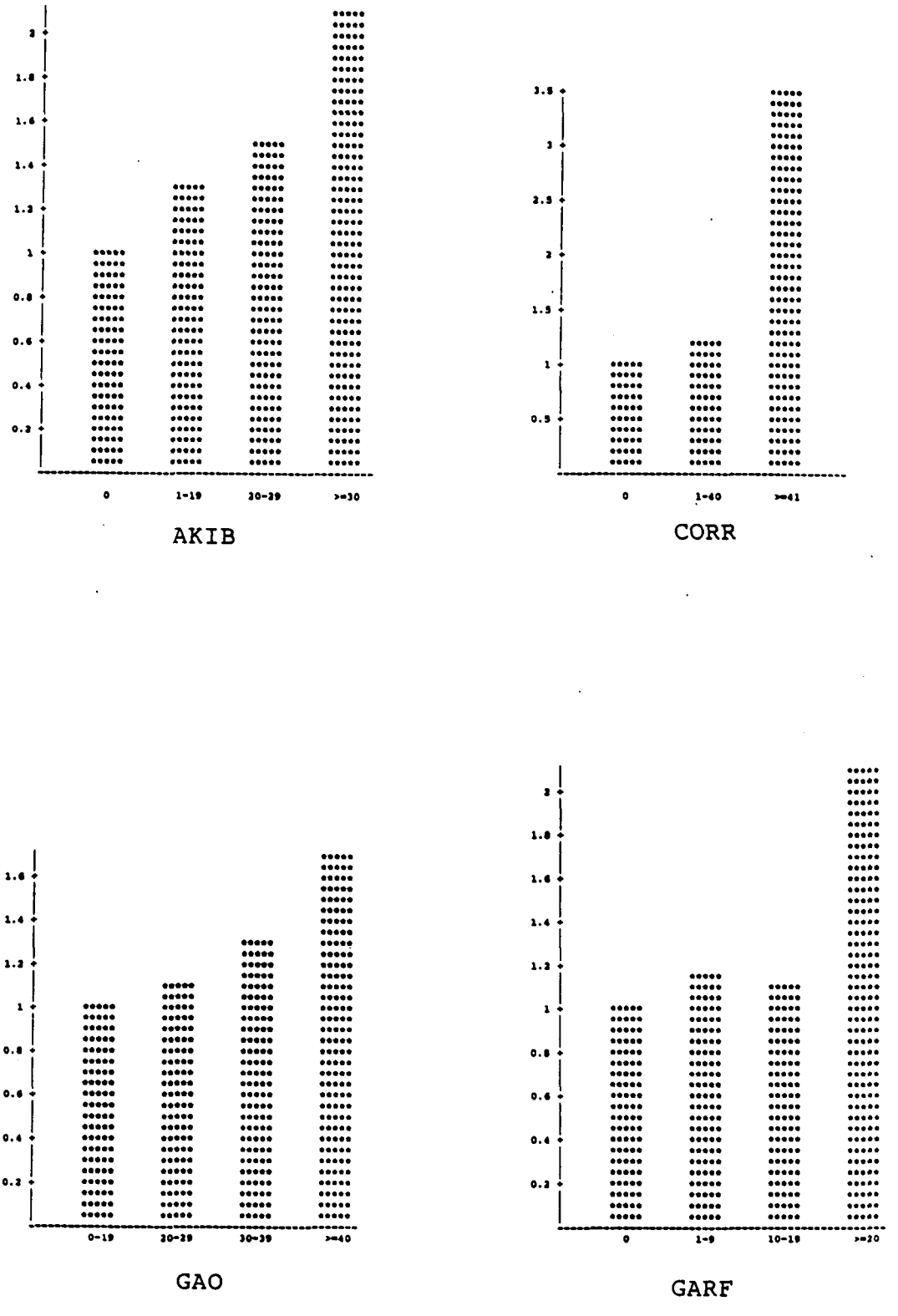
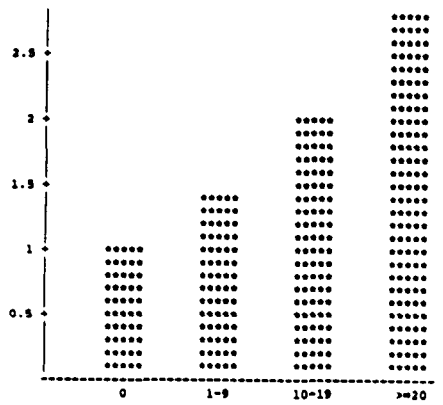
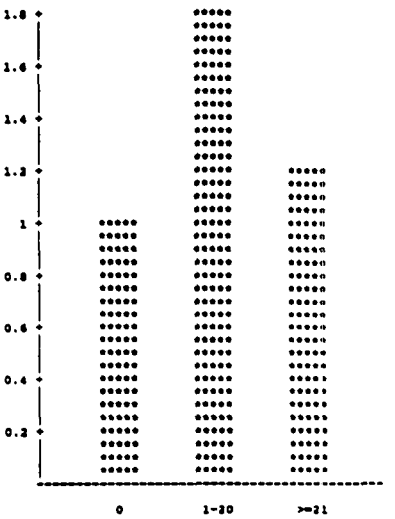


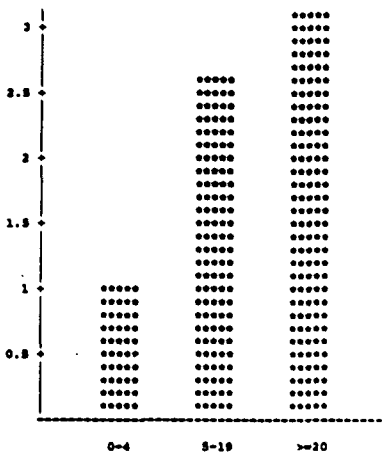
Figure 2-4. Plots of relative risk against exposure for studies in Table 2-7.



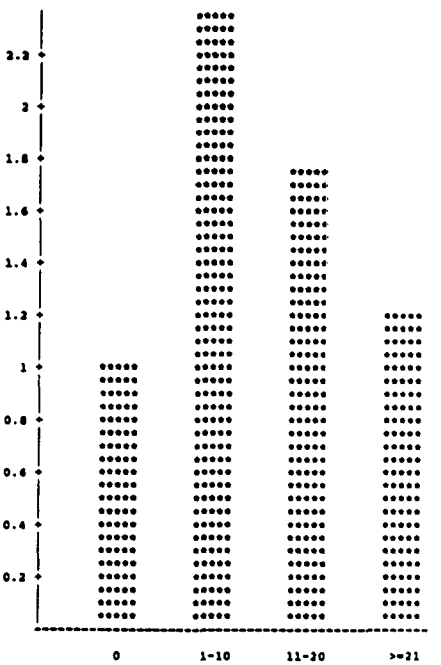
GENG



HUMB

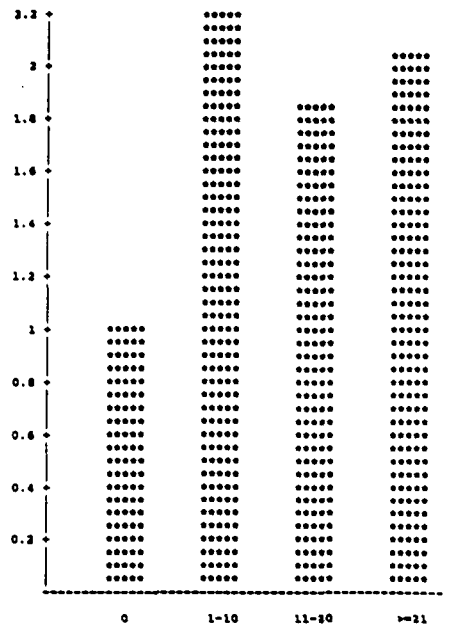


INOU

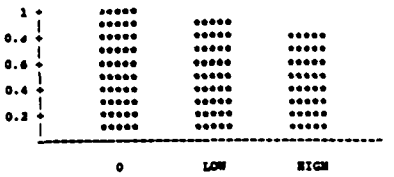


KOO

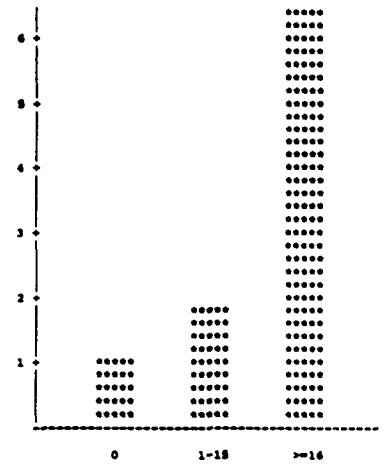
Figure 2-4. Continued.



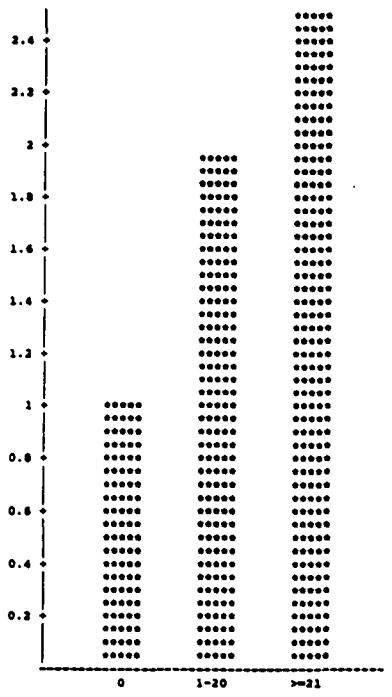
LAMT



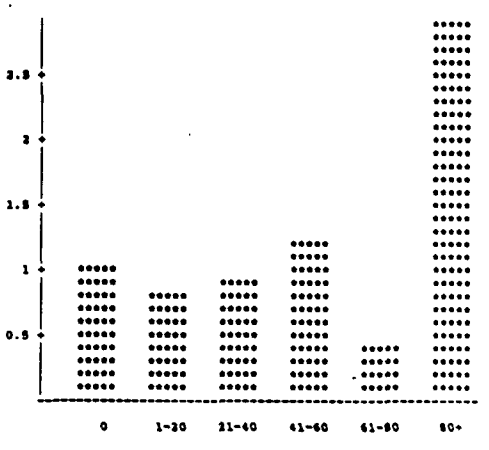
LEE



PERS



TRIC



VARE

Figure 2-4. Continued.

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APPENDIX

SUMMARY DESCRIPTIONS OF ELEVEN CASE CONTROL STUDIES

BROW. The case control study of risk factors for adenocarcinoma by Brownson et al. (1987) includes 23 never smoker cases (19 females) among the 102 cases interviewed. All subjects were white, had microscopically confirmed cancers incident from 1979 to 1982, and were identified through the Colorado Central Cancer Registry which covers the five county Denver metropolitan area. In the study as a whole, interviewed cases represented 68.5% of the 149 cases meeting eligibility criteria. Controls were chosen from persons with cancer at sites unassociated with cigarette smoking and were matched to the cases on age and sex. Of the 169 eligible controls, 131 (77.5%) were interviewed. Surrogate respondents were required for 69% of cases and 39% of controls.

Passive smoke exposure was analyzed both as a dichotomous variable based on the smoking status of the spouse and as a stratified variable based on the hours per day that the subject was in the presence of persons smoking. Other variables pertain to previous smoking, education, income, occupation, and residence history as an indirect measure of exposure to total suspended particulates.

The relative risk for adenocarcinoma among female never smokers exposed four or more hours per day relative to a lower exposure was 1.68 (95%CI= 0.39-2.97) after adjustment for age, income, and occupation. Similar nonsignificant risk estimates were shown when smoking by the spouse was considered as a dichotomous variable. The high proportion of surrogate source data led the authors to conduct parallel analyses limited to self-reported data. Results from those analyses were described as highly comparable and indicated possibly higher risks than those reported based for all respondents.

Note: The number (19 females) of never smokers in this study is much too small to make even a large observed relative risk (1.68) statistically significant. Further, combining ever smokers and never smokers (possibly to increase the sample size) makes the results difficult to compare with previous findings. After further adjusting the analysis for education and income, in addition to previous smoking habits and age, there was no indication of a potential association of lung cancer with ETS exposure.

GAO. Gao et al. (1987) report the results of a large (1407 subjects) population-based case control study of lung cancer etiology in Shanghai China, where lung cancer rates for women are among the highest in the world. Potential cases included all female patients with newly diagnosed primary lung cancer incident between February, 1984, and February, 1986, who were 35 to 69 years of age at the time of diagnosis and were residents of urban Shanghai. After exclusion of 93 patients who died, all remaining 672 cases were interviewed. Eighty-one percent were diagnosed by tissue biopsy or cytology and 19 percent by repeated x-ray. Adenocarcinoma was the predominant (61%) diagnosis. Controls were frequency matched within five-year age strata and randomly selected from the general population of the Shanghai urban area. Of the total of 735 controls interviewed, only 9.7% were secondary controls, chosen mainly because the first selected control had moved from the Shanghai urban area or was found to be outside the eligible age range. The study includes 246 cases and 375 controls who were nonsmokers (presumably had never smoked cigarettes). Logistic models were used to estimate relative risks of disease adjusted for other study factors.

Among all subjects no significant increase in risk was observed for overall ETS exposure during childhood (OR [odds ratio]=1.1, 95% CI=0.7-1.7) or adult life (OR=0.9, 95% CI=0.6-1.4). For these calculations, exposure was said to have occurred if the subject had ever lived with a smoker. However, when exposure was defined in

terms of husbands' smoking and the analysis was limited to nonsmoking women, lung cancer risks tended to increase with the number of years of exposure, with the highest observed risk (OR=1.7, 95%CI = 1.0-2.9) occurring in the comparison of those with 40+ years of exposure to those with 20- years exposure, after adjustment for age and education (p. 605, Table II) The relative risk in this comparison was higher (OR=2.9, 95% CI=1.0-8.9) for squamous-and-oat cell carcinoma alone. No test for trend over levels of ETS exposure was reported.

In the discussion of the results, the authors note the upward trend in risk associated with increasing years of exposure among nonsmoking women married to smokers. They conclude that ETS may be a contributing causative agent, but that other factors need to be considered as well, e.g., pre-existing lung disease, hormonal conditions, and especially exposure to cooking oil vapors.

Note: The study was not undertaken specifically to look at ETS lung association. Despite the large number of nonsmokers, it was not possible (or the authors chose not) to use women married to nonsmokers as a comparison group in their Table II. That may have been necessitated by the high prevalence of cigarette smoking among Chinese males.

GENG. In a brief article describing work similar in design and purpose to Gao et al, Geng et al. (1987) report the results of their study of lung cancer risk factors among women living in Tianjin, where the rates of lung cancer mortality are the highest in China. All 157 female cases were resident in Tianjin for at least ten years and were pair-matched to 157 controls for sex, race, age (within 2 years) and marital status. Diagnosis was predominantly by histologic or cytologic review (84.7%), although computerized tomography (10.8%) and clinical or x-ray (4.5%) methods were also used to identify cases. The authors describe the case group as representative of Tianjin female

lung cancer patients in terms of age and distribution of residents. They further state that the prevalence of smoking among the controls (40.8%) is similar to that seen among the Tianjin adult female population. The participation rates for cases and controls is not given, but other studies from China have reported very high response rates.

The study report available in the literature is fairly brief. Neither the method for assigning ETS exposure nor information about personal smoking status are discussed. Both multiple conditional regression and stratified analytic techniques were used to calculate reported risk estimates, but the authors do not stipulate which variables were controlled for the analyses.

The authors report that among the odds ratios of passive smoking from husbands, fathers, mothers, and colleagues, only that from husbands is significant. However, it is not clear whether this amount applies to smokers and nonsmokers combined in the same analysis or whether the analyses of ETS were restricted to nonsmokers only. The authors do explicitly state in Table 5 that the odds ratio for lung cancer in nonsmoking women married to smokers is 2.16 (95%CI=1.05-4.53), but it is not clear why this estimate differs from the odds ratio of 1.86 for nonsmoking wives with smoking husbands in Table 7. The odds ratios for lung cancer increase with the number of cigarettes smoked per day by the husband and the duration of exposure to the husband's smoking (Table 6). No tests for trend are provided, however, and whether these findings apply to all subjects as a group or only to the nonsmokers is not clear.

One interesting finding in Table 7 of this brief report is the similarity of estimated effects associated with ETS exposure from a husband only (OR=1.86, 95% CI= 1.04-3.5) and active smoking by the wife only (OR=2.61, 95% CI=1.4-4.6). Further,

these independent risks can be seen to interact on a multiplicative scale among smoking women married to smoking husbands (OR=4.9, 95% CI=1.8-9.5). Whether these estimates include adjustment for other factors is not stated.

HUMB. The study by Humble and colleagues (Humble, et al, 1987) includes 28 incident cases described by interview to be lifelong nonsmokers (8 men, 20 women). Cases were identified through the population-based New Mexico Tumor Registry while controls (130 men, 162 women) were chosen through randomly generated phone numbers and Health Care Financing Administration rosters of Medicare participants. Controls were frequency-matched to cases by ten-year age groups and by sex. Subjects were the nonsmoking subset in a larger study of lung cancer risk factors in which 88.5% of cases and 83.1% of controls eligible for interview had participated. Of the 28 lung cancers among nonsmokers, 24 had a histologic diagnosis in the Tumor Registry record. However, in a separate review of histologic materials for 17 of these cases, only eight cell types concurred with the Registry.

Subjects or their proxies were interviewed regarding their personal smoking habits, smoking by their spouses(s), and their occupational exposures. Surrogate interviews (usually with the spouse) were necessary for 19 of the 28 cases, but for only 13 of the 292 controls. No effect of information source was noted when analyses were run separately for self-reported and surrogate-reported cases using self-reported controls as the comparison group. Small numbers precluded a separate reporting of the odds ratio (OR) for males.

An elevated risk of lung cancer was reported for all subjects combined and for females separately. In logistic models, including adjustment for age and ethnicity and sex when appropriate, the ORs are 2.6 (90% CI = 1.2-5.6) for all subjects and 2.2 (CI=0.9-5.5) for females. Risk increased with the duration of spousal smoking (chi-

squared statistic for trend equals 2.01 for all subjects and 1.23 for females alone) in cross-tabular analyses, but not in results from multiple logistic models. No trend was seen over the average number of cigarettes smoked per day by the spouse. Separate analyses for current and former smokers revealed no increased risk associated with marriage to a smoker.

Cell-line specific analyses were precluded by the small number of cases with histologic confirmation of their diagnosis, the poor concordance of histologic designations in the Registry file, and the special review. The high proportion of cases with surrogate respondents may actually have improved the quality of data regarding exposure to a spouse's cigarette smoking, as spouses were the principal source of surrogate data. Exclusion of four former smokers (by information from other sources) did not alter the results. Size of the case series allowed only crude stratification of duration and amount when testing for trends, and may explain the marginal significance of findings reported separately for women.

INOU. In a large case control study of smoking and lung cancer in two Japanese cities, Inoue and Hirayama (1987) identified 37 women who died with lung cancer. Twenty-eight of these women (75.7%) were nonsmokers (definition not given). Cases were matched for age, year of death (within 2.5 years), and residential district to 74 controls who had died of cerebrovascular disease. Sixty-two (83.8%) of the controls were nonsmokers. Husbands' smoking status was available for 29 of the 37 cases and 54 of the 74 controls. Interviews were used to gather data for analysis, but the authors do not describe the characteristics or degree of relatedness of the surrogate respondents. Neither do they describe the degree of cooperation among the study subjects.

Mantel-Haenzsel odds ratios were used to estimate the relative risks of disease associated with ETS, adjusted for age alone and for age and residential district

(necessary given the different socio-economic natures of the two areas). With stratification for both age and district, the odds ratios are 2.58 (90% CI=0.44-5.7) when husbands smoked less than 19 cigarettes a day, and 3.09 (90% CI=1.04-11.81) when husbands smoked 20 or more cigarettes a day. The chi-squared test for trend is significiant ($p<0.05$).

LAMT. The large case control study by T.H. Lam and colleagues (Lam et al,, 1987) was undertaken to assess the respective roles of active and passive smoking in lung cancer etiology among women living in Hong Kong. Only patients with a pathologist's confirmation (98% by histological or cytological review) were included. Those with rare tumors, e.g., carcinoids, were excluded. Women were interviewed in hospital and then age-matched to healthy female controls selected from within their own neighborhoods. Interviews took place between 1983 and 1986 and approximately 99% of all eligible subjects responded.

Never smoker status for both subjects and their husbands was defined as having never smoked as much as one cigarette a day, or its equivalent in other tobacco products, for at least one year. A woman was considered exposed to her husband's tobacco smoke if she had lived with her smoking husband in the same household continuously for at least one year. If the husband was an ever- smoker, information on the type of tobacco and amount usually smoked per day by the husband and the duration of exposure was obtained. Never-married women were included as nonexposed to ETS. The authors describe the results of separate analyses on cigarettes only, and on all forms of tobacco, as similar and only report the latter. Relative risk (R) and 95% confidence intervals were calculated for each level of ETS exposure. Fisher's exact test (two-sided) was used to check whether the relative risk was significantly different from unity. Multivariate methods do no appear to have been used.

Among the total of 444 cases and 443 controls were 199 cases and 335 controls who had never smoked and for whom data on husbands' smoking were available. For never smokers the relative risk for lung cancer of all types from ETS exposure is 1.165 (95% CI=1.16-2.35); for adenocarcinoma the relative risk is 2.12 (95% CI=1.32-3.39). The risks for small and large cell carcinomas are 3.00 and 3.11, respectively, but these estimates are not statistically significant. Trends in relative risk for cancer at all sites, and for adenocarcinoma by the amount of tobacco smoked daily by the husband, are both significant with $P<0.001$. The authors discount the possibility that misclassification bias could have lead to the observed results, given the low prevalence of smoking (4.1%) among women in Hong Kong and the strength of the findings in the present study.

LAMW. The dissertation of Lam (Lam,W.K., 1985) was the third case control study of risk factors for lung cancer among females in Hong Kong. The nonsmoker cases, all with histologic or cytologic confirmation of adenocarcinoma, were part of a larger case series of 161 interviewed Chinese female lung cancer patients diagnosed at a large, regional general hospital with disease incident between January 1981 and April 1984. Fifteen cases with three other lung cancer histologies, as well as any patients with metastatic disease, were not included. Nonsmoking controls (n=144) were part of a larger series of 185 Chinese, mostly lower income female patients admitted to the orthopedic wards between 1982 and 1984. Cooperation of potential subjects exceeded 99%.

There was little difference in the ages, occupations, years of schooling, or recent residences of the 161 cases and 185 controls, so the author deemed it unnecessary to control for (stratify on) these variables in the analysis of the 60 nonsmoking cases with adenocarcinoma and 144 nonsmoking controls. Exposure to ETS was categorized

separately for husbands and other sources, e.g., cohabitating relatives or coworkers. Subjects were also queried regarding exposure to smoke from kerosene stoves and incense. The author interviewed all cases and, with a single research assistant, all controls. Thus, one may assume that interviews were not "blind".

The strongest and most statistically significant associations of ETS were with peripheral adenocarcinoma, with the highest odds ratio (2.64) occurring when exposure was based solely on husbands' smoking behavior. Relative risks of 1.6 and 1.7 were found for centrally located tumors when ETS was based on the husband's habits and total exposure to passive smoking, respectively. When data from Table 7.5 of the study are summed over sites, relative risks of approximately 2.0 are obtained with $P<0.05$, regardless of exposure classification scheme. All odds ratios appear to be unadjusted for any other study factors. No statistically significant risks from kerosene or incense were found. The author concludes that the small sample size and use of only a single hospital source for subjects are limitations.

SHIM. Shimizu and his colleagues (Shimizu et al., 1988) use a hospital-based case-control study of lung cancer in women to examine the effect of involuntary exposure to tobacco smoke from a variety of sources. Among 118 female patients with histologically confirmed lung cancer, 90 reported having never smoked cigarettes. Cases were matched on hospital, age (within 1 year), and date of admission to patients being seen for conditions generally unrelated to tobacco. All subjects were asked to complete a questionnaire about occupational history, kinds of fuels used for cooking and heating, and smoking habits, including number of cigarettes smoked daily by parents, siblings, the husband, and the husbands' parents in the home, as well as the amount of time spent in the same room with the husband, and the duration of marriage. ETS exposure at work was simply categorized by presence or absence of smokers.

No association was observed between risk of lung cancer and smoking by husbands, fathers, siblings, or coworkers. However, increased odds ratios were seen for smoking by subjects' mothers (OR=4.0, $P<0.05$) and by their husbands' fathers (OR=3.2, $P<0.005$). Dose-response relationships were not apparent for exposure by the mother or the husband's father, but the authors suggest that subjects may have been unable to recall the exact number of cigarettes in some cases (especially in childhood).

It is not clear whether variables such as occupational exposure to iron and other metals, or type of heating fuel, were assessed. Neither is there mention of cooperation rates by cases and controls. Adjustment of odds ratios for smoking by mother, smoking by husbands' father, and occupational exposures to iron and other metals, caused modest reductions in the point estimates, although smoking by husband's father in the home, (adjusted OR=3.2) is still significant with $P<0.005$. The authors describe this association as plausible since a high proportion of Japanese wives live with their in-laws after marriage and their father-in-law may have already retired.

SVEN. The study of lung cancer etiology in women by Svenson et al. (1988) includes 34 cases with microscopically confirmed non-carcinoid cancer who had never been regular smokers. Cases were patients referred to one of four clinical departments that diagnose or treat lung cancer in Stockholm county, Sweden. Only patients who would not benefit from specialist care, or who were not in physical or mental condition to allow an interview, were excluded from eligibility. Cases were matched on age using random selection from the population register in Stockholm County. For the whole study only seven subjects refused to be interviewed, resulting in a sample of 210 cases and 209 controls. Cooperation of nonsmoking cases and their matched controls was presumably high as well.

Four physicians completed all interviews using a structured questionnaire that included ETS exposure during childhood, as well as domestic and work environment exposure during adulthood. Other questions concerned the consumption of foods rich in vitamins A and C, and information about the dwellings where a subject had lived for more than two years. No surrogate sources of information were used and squamous/ small cell carcinomas constituted, respectively, 57.9% and 20.6% of the case histologies.

Women who lived with a smoking mother as children (R=3.3), or were exposed to ETS both at home and at work (R=2.1), or were exposed both as children and as adults (R=1.9), showed the highest risks. However, all estimates had very wide confidence intervals owing to the small sample size, and tests of association between ETS exposure and lung cancer incidence and tests for trend were all nonsignificant.

The authors describe the results for ETS as inconclusive, but note that most estimates of relative risk are greater than unity. The statistical power to detect an increased risk of 50% from exposure to ETS was only about 0.1. The author suggests that information bias may have precluded the identification of statistically significant small increases in risk. Specifically, no information on the duration or intensity of ETS exposure was obtained in the study, so it was difficult to assess the relative importance of domestic and workplace exposures.

VARE. The case control study described by Varela in his 1987 dissertation (Varela, 1987) is based on 439 histologically confirmed primary lung cancer cases incident in nonsmokers over an 18 month period in upstate New York. Sample size requirements were set large enough that detection of a relative risk of the size reported by Hirayama and Trichopoulos would be likely. However, to reach the calculated requirement of 450 matched case control pairs, it was necessary to include former smokers (55% of sample) in addition to never smokers. Cases were identified through a special rapid reporting

system in all participating hospitals and through periodic review of the New York State Cancer Registry. Controls were matched to cases on residence, age (within 5 years), sex, smoking history, and whether the interview was with the subject (67%) or with a surrogate for the subject (33%). Standardized interviews were conducted to collect data describing exposure to a spouse's cigarette smoke in terms of cigarettes/day, total years of smoke exposure, and total cigarettes smoked during the marriage. Information was also collected on total exposure from all smokers in the household, from coworkers on the job, and from exposure in social circumstances. The potentially confounding variables considered in the analysis include religion, income, marital status, other occupational exposures, and number of cigarettes smoked/day for former smokers. The study's total of 439 cases represents a cooperation rate of 84% among those selected for interviews. Approximately two potential controls had to be called per case to obtain enough study controls.

The author provides a systematic and exhaustive analysis based on linear logistic models for pairwise matched data. These data were collected as continuous values to allow analysis by source of exposure, e.g., spouse, other household smokers, coworkers, and social encounters, using methods for both continuous data and for categorical data. Analysis of household exposure was further complicated by the use of two alternative assumptions regarding missing data for exposure at previous residences.

After extensive analyses no index of exposure to spouse's tobacco or smoking by coworkers was associated with an increased risk for lung cancer. However, person-years of total exposure from all smoking household members showed a statistically significant linear trend. When exposure was fitted as a continuous variable, the unadjusted odds ratio associated with 150 person-years of exposure was 1.86 (95%CI=1.22-2.83). Adjustment for the potentially confounding variables listed above reduced the estimated OR for 150 person-years of exposure to 1.56 (95% CI=1.00-2.41). Exposure to passive smoke

in social situations showed an anomalous protective effect in both adjusted and unadjusted models (Tables 20,21,22 and Figures 25-28).

Note: The study contains extensive statistical analyses of which only a small part have been described here. When a large number of tests are made, the likelihood that one or more statistically significant result will occurr by chance alone increases. This can cause results to be interpreted as more significant than may be justified.

The author suggests that his own finding of no effect from exposure to spouses' smoke is understandable because the smoking habits of a spouse may not accurately describe true exposure to passive smoke. By contrast, the household exposure variable which was designed to more fully capture exposure in the home was the only index that was associated with increased risk of disease in this study. The greater association of household exposures with epidermoid and small cell histologies (Tables 12, 13, 15, 16) is not inconsistent with the apparent specificity of effect observed in PERS and GARF. One difficulty with comparing the Varela study with other case control studies is the inclusion of either males with females, or ex-smokers with never smokers, in the reported results. Although the analysis is very comprehensive, no reports for the risk of female never smokers alone were found. The author suggests that differences in past smoking habits of cases and controls may have a confounding effect. Although identical proportions of cases and controls were former smokers, cases had smoked a larger number of cigarettes per day (28.9 vs. 23.8, p=0.0002). Former smokers were not included, however, unless they had stopped smoking at least ten years prior to the interview. The author questions the validity of an apparent significant protective association from ETS in social circumstances, suggesting the possiblities of biased reporting and questionnaire artifacts as alternative explanations for this finding.

WU. Wu and her coauthors (Wu et. at., 1985) report the effects of ETS exposure as part of a larger study of determinants of lung cancer among white women living in Los Angeles County. Eligible cases included only patients with microscopically diagnosed primary adenocarcinoma (ADC) or small cell carcinoma (SCC) of the lung, incident between April 1, 1981 and August 31, 1982. Subjects also had to be English-speaking residents and less than 76 years old at the time of diagnosis. One neighborhood control was individually matched to each interviewed case using date of birth (within five years).

From a total of 490 eligible cases, 190 were dead or too ill to participate, eight could not be located and 44 refused to be interviewed, leaving 220 (44.9%) as the interviewed case group. After replacement of 85 potential controls who refused to participate, 220 controls were also interviewed. Surrogate respondents were not used because they were thought to be an unreliable source of information for ETS exposures and dietary practices in childhood.

Cases and controls were interviewed by telephone regarding personal smoking habits, exposure to ETS, history of lung diseases, dietary intake of vitamin A, types of heating and cooking fuels used, and reproductive history. Information obtained about childhood exposure to ETS included the amount and years of smoking by fathers, mothers, and other household members. Questions on exposure in adulthood pertained to smoking habits of spouses and other household members.

Study data were adjusted for potential confounding variables by application of logistic regresssion. Estimates for the relative risk of ADC are provided separately for nonsmokers, ex-smokers, and current smokers, but a small number of occurrences precluded the corresponding calculations for SCC. For ADC and SCC among smokers and nonsmokers combined, after adjustment for personal smoking habits, no

significantly increased risks were observed due to smoking by the subject's mother, father, spouse, or coworkers. For the 29 nonsmoking ADC cases, no significant elevated risk was associated with ETS exposure from either parent (R=0.6, 95% CI=0.2-1.7), from spouses(s) (R=1.2, CI=0.5-3.3), or from the workplace (R=1.3, CI=0.5-3.3). The observed relative risk for ADC increases with the number of years of adult ETS exposure from spouse(s) and coworkers, but a test for trend is not statistically significant.

The authors attribute the ambiguous nature of their results to the lesser etiologic role of ETS for ADC compared to SCC. Further, 12 (41%) of the 29 ADC cases are bronchoalveolar cell carcinomas, which Correa et al. (1983) found to have a relatively weaker association with passive smoking.