Exposure Misclassification Bias in Studies of Environmental Tobacco Smoke and Lung Cancer

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It is now recognized that exposure to environmental tobacco smoke (ETS) in the workplace and other settings outside the home may be equally as important as residential ETS exposure. This review examines the sources of misclassification in the assessment of workplace ETS exposure in questionnaire-based epidemiologic studies. Cogent to this discussion is the role of misclassification of ever smokers as never smokers, which is important in studies of both workplace and residential ETS exposure and lung cancer and is discussed first. The collective evidence from studies that have used direct or indirect approaches to estimate smoker misclassification shows that although some misclassification of ever smokers as never smokers exists in studies of ETS and lung cancer, the potential bias from the misclassification of smokers is unlikely to explain the observed increased risk of lung cancer associated with ETS exposure. *Key words*: environmental tobacco smoke, exposure misclassification, lung cancer. — *Environ Health Perspect* 107(suppl 6):873–877 (1999). *http://ehpnet1.niehs.nih.gov/docs/1999/suppl-6/873-877wu/abstract.html*

In epidemiologic studies of environmental tobacco smoke (ETS) and lung cancer, the problem of misclassification and the potential for resulting bias continue to be a concern. This article covers two specific sources of misclassification of exposure in studies of ETS and lung cancer: misclassification of ever smokers as never smokers and misclassification of workplace ETS exposure. Although residential ETS exposure may also be misclassified, this is a separate topic covered in other reviews and is not discussed here. The misclassification of ever smokers as never smokers is an important concern in any study of ETS exposure and lung cancer and is discussed first. We specifically examine the parameters that determine this source of bias. Sources of misclassification in the questionnaire approach to assess workplace ETS exposure are discussed.

Misclassification of Ever Smokers As Never Smokers

In epidemiologic studies of ETS and lung cancer, it is critical that the classification of participants as never smokers is accurate (*1,2*). In the 1986 National Research Council (NRC) report (*1*) and a subsequent article, Wald et al. (*2*) pointed out that because smokers tend to marry smokers, if a study contains subjects classified as never smokers when they are smokers, these subjects are more likely to be classified as exposed to ETS, and thus the study is likely to overestimate the risk associated with ETS exposure due to the increased risk of lung cancer associated with active smoking. Whether and how much of the observed increase in risk of lung cancer associated with ETS exposure may be explained by this source of bias is controversial. Lee (*3*) has argued that the occurrence of this misclassification is high (about 12% among never smokers) and might explain all or most of the observed association between spousal smoking and risk of lung cancer in never smokers. Conversely, the NRC report (*1*) and other investigators (*2,4*) concluded that the occurrence of smoker misclassification is relatively low (about 5%) and cannot account for the observed effect of ETS on lung cancer risk. Wald and co-workers (*2*) have proposed that this misclassification increases with increasing values of four determinants: the proportion of ever smokers misclassified as never smokers; the risk of lung cancer in current and former smokers misclassified as never smokers; the aggregation of smokers; and the prevalence of smoking in the population under investigation. Divergence of opinion has arisen in part because different parameters have been used to determine this bias. In addition, there is no consensus regarding the best estimate of each of the parameters that in combination determine smoker misclassification. Different modeling approaches have been developed by Wald (*1,2*), Wells and Stewart [described in the U.S. Environmental Protection Agency (U.S. EPA) report (*5*)], Lee and Forey (*6*), Tweedie and Mengersen (*7*), and Biggerstaff (*8*) to estimate the extent of bias. The merits and limitations of these various approaches will not be covered in this article.

The Proportion of Ever Smokers Reported as Never Smokers

Two main types of studies have provided information regarding the proportion of ever smokers who are misclassified as never smokers. The first type of study compares the concordance of self-reported smoking status obtained on two occasions over time, typically at least 5 years between resurveys. Most of these studies have found that approximately 5% of ever smokers are misclassifed as never smokers (*3,5,9,10*) (Table 1). This finding is generally comparable in men and women and in studies conducted in different countries. An exception is the higher misclassification rate reported among male smokers in one study (*3*). In the largest study published to date on this topic, information on smoking habits was obtained on two occasions from approximately 18,000 Swedish twins born between 1886 and 1925 (cohort I) and approximately 22,000 Swedes born between 1914 and 1945 who were randomly selected from the general population (cohort II) (*10*). Smoker misclassifications in cohort I and cohort II were 4.9 and 5.0%, respectively, for men and 4.5 and 7.3%, respectively, for women (*10*).

Although the percentage of misclassified ever smokers (Table 1) is unlikely to depend on the smoking prevalences in the population, the proportion of never smokers misclassified as smokers (Table 2), which can be also calculated in the studies of ever smokers, does depend on the prevalence of smoking in the population under study. This point is illustrated in the data shown in Table 2. A higher rate of misclassification may be obtained for never smokers with lung cancer than for controls comprising never smokers because of a smaller proportion of never smokers among cases. Similarly, a higher rate of misclassification may be observed for men than for women because of a smaller proportion of never smokers among men (*3,10–12*) (Table 2). As shown in Table 2, the substantial variability in the percentage of nonsmokers misclassified as smokers (11–23% in males and 2–5% in females) contrasts with the relative stability of the proportion of ever smokers misclassified as never smokers (Table 1). Using the Swedish cohort mentioned previously, misclassifications of never smokers as smokers in cohort I and cohort II were 11.1 and 11.5%, respectively, for men and 1.3 and 2.2%, respectively, for women (*10*). Thus, misleading conclusions may be reached if the rate of never smoker misclassification is used

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Table 1. Misclassification of ever smokers as never smokers.

Study (reference)	Locale	Sex	Ever smokers misclassified as never smokers (%)
Lee, 1992 (*3*)[a]	Scotland	F	4.9
		M	12.9
U.S. EPA, 1993 (*5*)[b]	U.S. U.K. Japan	F	3.7
Britten, 1988 (*9*)	U.K.	F + M	5.1
Nyberg et al., 1997 (*10*)	Sweden Cohort I	F	4.5
		M	4.9
	Sweden Cohort II	F	7.3
		M	5.0

Abbreviations: F, female; M, male. [a]Unpublished results of Hebert and Fry cited in Table 3.33 of Lee (*3*). [b]Based on results presented in Table B-4 of the U.S. EPA report (*15*), excluding the data from Britten (*9*), presented separately in this table.

Table 2. Misclassification of never smokers as ever smokers.

Study (reference)	Locale	Never smokers misclassified as ever smokers (%) Male	Female
Akiba et al., 1986 (*11*)	Japan	23.4	–
Lee, 1992 (*3*)	Scotland	14.4	4.8
McLaughlin et al., 1987 (*12*)	U.S.	11.6	3.9
Nyberg et al., 1997 (*10*)	Sweden	11.3[a]	1.7[a]

–, no data. [a]This represents an average of the percent misclassification found in cohort I and cohort II.

as one of the determinants to determine smoker misclassification.

One approach for calculating the proportion of self-reported nonsmokers who are in fact current smokers is to validate the smoking status by measuring biomarkers such as cotinine and/or nicotine levels in biologic fluids (*5,13–23*) (Table 3). Cotinine is a well-established, sensitive, and specific biomarker of recent exposure to tobacco smoke (*24*). There is consensus that cotinine levels in current smokers are at least several hundred times higher than the levels in nonsmokers (*5,13*). A large number of biomarker studies have found that approximately 3% of nonsmokers have cotinine/nicotine levels inconsistent with levels in true nonsmokers (Table 3). This collective evidence is based on cross-sectional data collected from more than 4,000 nonsmokers of diverse demographic backgrounds who have participated in studies conducted in different countries. Approximately one-third of these data is from a large collaborative study conducted in 13 study centers covering 10 countries that used identical study protocols to investigate the relationship between recent (i.e., for 8 days preceding the interview) ETS exposure from residential and nonresidential sources according to self-report and urinary cotinine concentrations (*14*). In the only case–control study of ETS and lung cancer that also determined urinary cotinine levels in cases and controls as a marker of recent exposure to tobacco smoke (*25*), the percentage of smoking cases and controls misclassified as never smokers (i.e., urinary concentrations exceeding 55 ng/mg of cotinine/creatinine) were 3.1 and 5.0%, respectively. Thus, biochemically validated analyses of self-reported data on ETS exposure obtained from both case–control (*25*) and cross-sectional studies (Table 3) confirm that only a small proportion of nonsmokers is misclassified as smokers.

Table 3. Proportion of nonsmokers (never or former smokers) who are probable current smokers according to cotinine or nicotine concentrations.

Hackshaw et al. (*13*)	
	6 studies,[a] included 1,682 nonsmokers
	33 nonsmokers or 2.0% were misclassified (>10% of median or mean concentration in active smokers)
U.S. EPA - Table B-3 (*5*)	
	3 studies,[b] included 1,145 nonsmokers (844 never smokers, 301 former smokers)
	45 nonsmokers (3.9%) were misclassified (>10% of cotinine levels of current smokers)
Riboli et al. (*14*)—Collaborative IARC study	
	13 centers in 10 countries including 1,369 nonsmoking women
	47 women (3.4%) were misclassified (values of cotinine/creatinine above 50 ng/mg)

Abbreviations: IARC, International Agency for Research on Cancer. [a]Included Feyerabend et al. (*15*), Wald and Ritchie (*16*), Pojer et al. (*17*), Haddow et al. (*18*), Lee (*19*), and Thompson et al. (*20*). [b]Included Coultas et al. (*21*), Cummings et al. (*22*), and Pierce et al. (*23*).

The Risk of Lung Cancer in Current and Former Smokers Misclassified As Never Smokers

The magnitude of misclassification bias is also influenced by the risk of lung cancer among current and former smokers misclassified as never smokers. Wald and co-workers (*2*) and Hackshaw et al. (*13*) estimated that ever smokers misclassified as never smokers experience a 2- to 3-fold higher risk of lung cancer than true never smokers. Their estimate was based on the assumption that most misclassified current or former smokers are light smokers and thus would have only a fraction of the risk of continuing smokers. There is ample evidence showing that misclassified ever smokers are indeed lighter smokers who have started smoking later, smoked fewer cigarettes for fewer years, and were less likely to inhale when they smoked (*9,10,26*). More recently, results from the Swedish twin cohort (cohort I) provided, for the first time, a direct estimate of the risk of lung cancer among misclassified ever smokers (*10*). Nyberg et al. (*10*) found that the risk of lung cancer among misclassified male smokers (relative risk [RR] = 1.9) was between that of never smokers (RR = 1.0) and former smokers (RR = 4.3) and was substantially lower than that of current smokers (RR = 13.3). Although the estimate of the risk among misclassified male smokers was based on a small number of lung cancer cases and there were no lung cancer cases identified among misclassified female smokers to conduct a comparable analysis, results from this Swedish cohort corroborate that the risk of lung cancer among misclassified smokers is no more than about 2-fold, which is compatible with the estimates used by Wald and co-workers (*2*) and Hackshaw et al. (*13*) in their studies of smoker misclassification

Aggregation of Smokers

A third parameter that influences the smoker misclassification bias is the aggregation of smokers, i.e., the extent to which smokers live with other smokers. Although the majority of lung cancer studies in nonsmokers were conducted among women never smokers with lung cancer, studies including both males and females were used to calculate this concordance ratio, which has been expressed numerically as the odds ratio in a 2 × 2 table that categorized the index subject and his/her cohabitant by their respective smoking status. This concordance ratio of never smoked/ever smoked has been found to be between 2 and 4 in about 20 studies; most investigators regard a figure close to 3 as the best estimate (*2,5,6,13*). Not surprisingly, the concordance ratio depends on the demographic profile of the population under study (e.g., age, gender, race) and the specific questions that are asked regarding smoking habits (e.g., current versus ever smoker, definition of never smoker).

Smoking Prevalence in the Population under Study

The proportions of men and women in the population who have smoked at any time influence the extent of the misclassification; the greater the proportions, the greater the bias (*2,13*). There is usually little controversy regarding the smoking prevalence for a particular population under study (assuming the information is available). However, because the prevalence of smoking differs among populations, countries, and calendar times, this parameter has raised discussion primarily in pooled analyses of studies of ETS and lung cancer. In the U.S. EPA report (*5*),

Wells and Stewart recommended using the smoking prevalence of each individual study whenever possible or at least selecting smoking prevalence(s) to represent the population(s) under investigation.

Sensitivity analyses have been conducted (*2,13*) to examine the effect of each of these parameters on the magnitude of misclassification bias. Hackshaw et al. (*13*) showed that an RR of 1.24 for lung cancer associated with ETS exposure (determined in a meta-analysis of about 40 studies) would be reduced only slightly (to an RR of 1.18) and remain statistically significant under conservative but probable estimates for the different parameters of interest: an aggregation ratio of 3, the proportion of ever smokers misclassified as never smokers 7%, and an RR of 3.0 for lung cancer among smokers misclassified as never smokers. Conversely, the RR of 1.24 would be reduced to a nonsignificant RR of 1.11 if the risk of lung cancer among misclassified ever smokers were 4.0, if 9% of ever smokers were misclassified as never smokers, and if the aggregation ratio were 3.0. This RR is further reduced to 1.08 if the aggregation ratio is increased to 4.0. As discussed above, there is little evidence to suggest that these high parameter values are operating in a majority of studies that have investigated the role of ETS and lung cancer.

The above indirect approach to estimate smoker misclassification is complemented by a recent study (*26*) that used a direct approach to investigate the effect of misclassification bias on the estimate of lung cancer risk associated with ETS. This validity study was conducted in the Swedish, Spanish, and Italian study centers that were part of a European multicenter case–control study of ETS and lung cancer (*27*). Next of kin of the index subjects (n = 408; 175 cases, 233 controls) were contacted and interviewed regarding the smoking status of the index subject either on the same day that the index subject was interviewed or at least 4 months after the interview with the index subject. Quantitative smoking information was collected from 351 index subjects who reported being never smokers (i.e., defined as having smoked 400 or fewer cigarettes over lifetime) and their next of kin (i.e., the smoking habits of 57 index subjects could not be independently confirmed by their next of kin). Nine of the 351 index subjects (2.0% among cases; 3.1% among controls) were reported by their next of kin to be occasional smokers (i.e., smoked more than 400 cigarettes over lifetime). The RR estimates for lung cancer associated with ETS exposure from spouses and at work were not changed in multivariate analyses after excluding the 9 subjects who were possibly misclassified. For example, the RR for ever exposed to spouse who smoked was 1.29 for the total population (i.e., 351 subjects) and 1.30 when the 9 subjects who were potentially misclassified were excluded. The corresponding RR estimates associated with ETS exposure in the workplace were 1.48 and 1.41; the RR estimates associated with ETS exposure from spouses or in the workplace were 1.73 and 1.70. Thus, this multicenter case–control study found an equally low proportion of misclassified ever-regular smokers among reported case and control never smokers. Accordingly, estimates of the effects of ETS changed minimally after exclusion of the potentially misclassified subjects.

In summary, since the recognition of misclassification of ever smokers as never smokers as a potential source of bias in studies of ETS and lung cancer, concerted efforts have been made to determine the extent of this problem. Several large, well-designed and well-conducted studies confirmed that the proportion of ever smokers reported as never smokers (*10*), the proportion of nonsmokers misclassified as ever smokers (based on cotinine measurements) (*14,25*), and the risk of lung cancer among misclassified smokers (*10*) are all low, in agreement with the conclusion of the NRC in 1986 that smoker misclassification cannot explain the ETS effect on lung cancer risk in never smokers (*1*). In addition, the risk of lung cancer associated with ETS exposure was essentially unaffected by misclassification bias in the only study that has directly evaluated its potential impact (*26*).

Misclassification of ETS Exposure at the Workplace

To determine the association between ETS exposure and risk of lung cancer, earlier researchers focused primarily on ETS exposure inside the home (*1,28*). However, large cross-sectional studies show convincingly that ETS exposure in the workplace and other settings outside the home may be equally as important as ETS exposure inside the home (*29*). In the Third National Health and Nutrition Examination Survey (NHANES III), which included a large representative sample of the U.S. population, nearly 40% of U.S. workers who were nontobacco users reported ETS in the workplace (*30*). Among those who reported workplace ETS exposure only, serum cotinine levels were significantly higher than in individuals reporting no exposure at work and at home; these higher levels also were about half the levels of those individuals reporting home ETS exposure only (*30*).

In published epidemiologic studies of lung cancer, data on ETS exposure come solely from questionnaires completed by either the index subjects or the suitable next of kin. In the next section, we review measures of workplace ETS exposure that have been included in epidemiologic studies of lung cancer and the sources of misclassification of workplace ETS exposure.

Measures of Workplace ETS Exposure in Published Lung Cancer Studies

The questionnaire method that has been used to assess ETS exposure in the workplace is similar to that used to assess ETS exposure from spouses. For example, to assess ETS exposure from spouses/cohabitants, most studies included questions about smoking habits of all or those of the current spouse/cohabitant of longest duration. Information on the extent of exposure was based on the duration of smoking and/or the number of cigarettes/tobacco products smoked by spouses or cohabitants (*1,5,28, 29*). Similar approaches have been used to ascertain workplace ETS exposure, although the questions asked in the studies published to

Table 4. Studies on ETS exposure in the workplace and risk of lung cancer in lifetime nonsmokers.

Study (reference)	Type of questions asked
Fontham et al., 1994 (*25*) Boffetta et al., 1998 (*27*) Wu et al.,1985 (*31*) Wu-Williams et al., 1990 (*32*)	Lifetime occupational history—ETS exposure at each job including yes/no exposure; hours of exposure per day, and number of smokers
Brownson et al., 1992 (*33*) Kabat and Wynder, 1984 (*34*) Kalandidi et al., 1990 (*35*) Shimizu et al., 1988 (*36*)	ETS exposure at current/last job (yes/no)
Garfinkel et al., 1985 (*37*)	Average number of hours of ETS exposure at work during past 5 and past 25 years
Janerich et al., 1990 (*38*)	Number of smokers at work; amount of time worked with smokers
Kabat et al., 1995 (*39*)	4 jobs lasting >1 year: hr/week of ETS exposure; years started/stopped; number of smokers; average no. of smokers within 10 ft
Ger et al., 1993 (*40*)	Co-workers smoked for >1 year in their presence, at least 5 hr/day
Lee et al., 1986 (*41*)	Timing not specified; rated exposure as no, little, a lot
Ko et al., 1997 (*42*) Koo et al., 1987 (*43*)	Exposure at work (yes/no and years of exposure)
Stockwell et al., 1992 (*44*) Schwartz et al., 1996 (*45*) Zaridze et al., 1998 (*46*)	Not certain

date have varied (Table 4). A few studies attempted to ask about lifetime workplace ETS exposure (*25,27,31,32*). In these studies, subjects were asked about each job they had and whether they were exposed to ETS at each job. However, in other studies, information on ETS exposure in the workplace was requested only for selected jobs [e.g., current or last job (*33–36*), four jobs lasting at least 1 year (*39*), jobs for selected periods (e.g., during past 5 and past 25 years) (*37*)], or for a specific definition of ETS exposure [e.g., co-workers smoked for at least 1 year in the presence of the subject (*40*)]. In addition, some studies only classified exposure in a dichotomized manner (yes/no) (*33–36,40,42*), whereas others attempted to assess the intensity of exposure (*25,27,31,37–39,41*) such as by cumulating the years of workplace ETS exposure (*25*). In one study, a combined quantitative measure for workplace ETS exposure was determined on the basis of the total number of years of exposure weighted by the number of hours of exposure per day and a subjective index of smokiness in the workplace (*27*).

Sources of Misclassification of Workplace ETS Exposure

Misclassification of workplace ETS exposure may occur if the exposure cannot be reported accurately. Inaccuracy in report may be due to lack of knowledge or difficulty in recalling the exposure of interest. Because lung cancer is a rapidly fatal disease, some studies included a high percentage of surrogate respondents (*33,37,38,44,45*). Reliable assessment of workplace ETS exposure is a particular concern in these studies since surrogates may be less able to provide information on the subjects' exposure to ETS in the workplace. The strongest support for the association between workplace ETS exposure and an increased risk of lung cancer in nonsmokers comes from epidemiologic studies in which only self-respondents (*27,31*) or a high percentage of self-respondents (*25*) were included. Misclassification is a particular concern if there is differential recall of exposure between lung cancer cases and controls (*47*).

Few test–retest studies of questionnaire reports (*48–50*) assess the reliability of self-report of ETS exposure, and only one of these studies specifically examined workplace ETS exposure (*48*). We first considered the results on residential exposure to ETS, knowing that these results may not be directly applicable to studies of workplace ETS exposure. These studies confirm that self-reports of any (yes/no) residential exposure to ETS from spouses and from parents were generally reliable but that the quantitative assessment of exposure, i.e., number and duration of the exposure, was reported less reliably (*48–50*). One study (*48*) examined the reliability of responses on ETS exposure in the workplace among 117 control participants (49 never smokers, 68 ever smokers) of a case–control study of lung cancer. Among the never smokers in this study (the relevant subgroup in studies of ETS and lung cancer), good agreement was found for responses to questions on residential ETS exposure. (The kappa statistics were 0.66 and 0.69 for female and male nonsmokers, respectively.) There was also good agreement of responses to questions on workplace ETS exposure (kappa statistic 0.76) among female nonsmokers, but agreement was poor among male respondents (kappa statistic –0.08). This finding, based on only nine male nonsmokers, cannot be considered conclusive.

Misclassification of ETS exposure in the workplace may also occur if the assessment of this source of exposure is incomplete. Although the questionnaire-based approach has been used very successfully to obtain information on lifetime occupations and select exposures, assessment of workplace ETS exposure is complicated by the heterogeneity of this exposure. In a review of short-term studies that have used nicotine or other tracers to directly measure ETS exposure in offices, hospitals, restaurants, bars, airplanes, and diverse blue-collar occupations, Hammond (*51*) concluded that workplace ETS exposures are highly variable and that the average workplace concentrations of ETS are often greater—as much as 10-fold higher—than the concentrations in homes. Heterogeneity in workplace ETS exposure exists, in part, as a result of diverse time–activity patterns, different and changing policies regarding the use of tobacco products in work settings, and other parameters (*52*). A better understanding of the distributions of ETS exposure for U.S. workers is now emerging from studies that have used mathematical models (i.e., mass–balance models) to predict exposure patterns (*53*) or from studies that have determined exposure patterns, using personal or area monitoring techniques (*51*). The challenge remains for epidemiologists to integrate this information to fill the gaps and to overcome limitations of the traditional questionnaire approaches in assessing workplace ETS exposure.

Summary

It is evident that some misclassification of ever smokers as never smokers exists in studies of the health effects of ETS. Both direct and indirect approaches (*1,10,13,14,26*) have been used to estimate smoker misclassification, and they confirm that the potential bias due to smoker misclassification is unlikely to explain the observed increased risk of lung cancer associated with ETS exposure. Exposure to ETS in the workplace is now recognized as a major source of ETS exposure outside the home. The specific questions that were asked in order to ascertain workplace ETS exposure have varied in questionnaire-based studies. The approach has ranged from very crude assessment of any exposure at single or selected jobs to detailed assessment of exposure in all jobs, with consideration of intensity of exposure. The levels of workplace ETS exposure are likely to vary, depending primarily on whether there is any restriction of tobacco smoking and the nature and enforcement of such restrictions, as well as the environmental conditions of the workplace if tobacco smoking is allowed. Because of recent workplace restrictions of tobacco smoke in the United States and outside the United States, it is particularly important that researchers who study the association between lung cancer and workplace ETS exposure design questions specifically suited for the populations under study to minimize potential misclassification of occupational ETS exposure.

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