Lung Cancer and Environmental Tobacco Smoke: Occupational Risk to Nonsmokers

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The principal epidemiologic evidence that environmental tobacco smoke (ETS) increases the risk of lung cancer in (lifelong) nonsmokers is from studies of nonsmoking women married to smokers. This article estimates exposure–response curves for 14 studies (1,249+ cases, 7 countries) with data on lung cancer categorized by the number of cigarettes/day smoked by the husband. The pooled results from the five U.S. studies alone are extrapolated to ETS levels in the workplace using measures of serum cotinine and nicotine samples from personal monitors as markers of exposure to ETS. It is predicted that the increase in lung cancer risk for nonsmoking women from average ETS exposure at work (among those exposed at work) is on the order of 25% (95% confidence interval (CI) = 8, 41) relative to background risk (i.e., with no ETS exposure from any source). This compares to an estimate of 39% (95% CI = 5, 65) for nonsmoking women whose husbands smoke at the adult male smoker's average of 25 cigarettes/day. At the 95th percentiles of exposure, the estimate from spousal smoking is 85% (95% CI = 32, 156), compared to 91% (95% CI = 34, 167) from workplace ETS exposure. Subject to the validity of the assumptions required in this approach, the outcome supports the conclusion that there is a significant excess risk from occupational exposure to ETS. The excess risk from ETS at work is typically lower than that from spousal smoking, but may be higher at the 95th percentiles of exposure. *Key words*: dose response, environmental tobacco smoke, lung cancer, occupational risk. — *Environ Health Perspect* 107(suppl 6):885–890 (1999).
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There is considerable evidence that exposure to environmental tobacco smoke (ETS) poses a risk of lung cancer to nonsmokers (defined as lifelong nonsmokers) based on the relationship between active smoking and lung cancer, the presence of known and suspected carcinogens in ETS, and evidence from epidemiologic studies showing an increased risk of lung cancer to nonsmoking women married to smokers (*1*). Given an association between spousal smoking and lung cancer incidence in nonsmokers, it is reasonable to expect an association between occupational exposure to ETS and lung cancer in nonsmokers as well. Unlike studies of exposure to spousal smoking, however, where the number of cigarettes smoked per day by the husband is a common surrogate for ETS exposure, it is difficult to measure occupational exposure and to make comparisons across studies. Additionally, the number of studies with direct observations on occupational exposure is limited and some are from outside the United States where occupational exposure to ETS may differ from that inside the United States. Statistically combining the outcomes from these studies (meta-analysis) has produced varied results, with only one study reporting a significant risk of lung cancer from occupational exposure to ETS (*2*).

For the safety and protection of nonsmokers who may be exposed to ETS in the workplace, it is imperative to gain a better understanding of the potential lung cancer risk associated with occupational exposure to ETS. Toward that end, the current analysis brings to bear the results of those epidemiologic studies on nonsmoking women married to smokers that contain exposure–response data (i.e., where presence/absence of lung cancer in study participants is categorized by the number of cigarettes smoked per day by the spouse). Exposure–response relationships are calculated for individual studies using regression analysis and then combined across studies by methods for meta-regression. The assumption is made that the expected value of the natural logarithm of relative risk [ln(RR)] is proportional to the number of cigarettes smoked by the husband.

The exposure–response model for the U.S. studies alone is extrapolated to risk from occupational exposure to ETS, which requires a second assumption: Among nonsmoking women exposed to ETS at home (married or not), the excess risk attributable to the mean exposure at home, as determined by measures of serum cotinine, is equal to the excess risk from spousal smoking at the average rate of adult male smokers—about 24 cigarettes/day. ETS exposure in the workplace, relative to the home, is then determined from data on serum cotinine as well and from data on airborne nicotine collected by personal monitors. In principle, the current approach extends that of Hackshaw et al. (*3*). Their objective was to estimate the risk of lung cancer in nonsmoking women married to smokers by linear extrapolation from the exposure–response relationship for smokers. Our objective is to estimate the risk of lung cancer from ETS in the workplace by extrapolation from the exposure–response relationship for nonsmoking women married to smokers. The value of this method is that it adds a new approach with different data to estimation of risk from ETS in the workplace and contributes to the growing pool of evidence on this important topic.

Methods

A search of former reviews and electronic databases located 18 epidemiologic studies with data relating lung cancer in nonsmoking women to the number of cigarettes smoked per day by the husbands. No attempt was made to locate unpublished manuscripts or data published in conferences/meetings that might minimize potential publication bias. Two criteria were used for inclusion of studies: *a*) the study was not conducted in a locale where other indoor pollutants might mask an ETS effect; *b*) the description of the study suggests adequate attention to design, execution, and interpretation of data. Criterion *a*) eliminated two studies (*4,5*), and Criterion *b*) eliminated two more (*6,7*). Studies by Wang et al. (*4*) and Liu et al. (*5*) were conducted in locations in China where indoor environments are often polluted by fumes from cooking oils or by coal smoke. Studies by Inoue and Hirayama (*7*) and Geng et al. (*6*) lack sufficient descriptions for evaluation. The 14 remaining studies included in the analysis are listed in Table 1. Relative risks from cohort studies and odds ratios from case–control studies are both referred to as RRs for editorial convenience.

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For each of the 14 studies, an exposure–response relationship is estimated where response refers to lung cancer in nonsmoking women married to smokers and exposure refers to the number of cigarettes per day smoked by their husbands. A log-linear fixed-effects model is assumed, as described by Berlin et al. (*8*):

$$E(lnRR) = \beta X \qquad [1]$$

where *lnRR* is the natural logarithm of relative risk, *X* is the number of cigarettes/day smoked by the husband, and β is the unknown slope parameter of the regression. This model was previously applied by Hacksaw et al. (*3*) to affirm the conclusion of a significant lung cancer risk from spousal smoking. In the current analysis the combined regression from studies in the United States alone is considered most suitable for extrapolation of risk to occupational exposure in the United States. Exposure–response relationships, however, are calculated for all countries for which there are suitable data. A test of heterogeneity and plots of the country-wide regressions are used to check that the result for the United States appears reasonable compared with those of other countries.

Within a given study, the RRs [and hence the ln(RR)s] at different exposure levels within a study are correlated because they use the same referent group (*8*). If that correlation is ignored, the slope of the regression for ln(RR) will still be unbiased, but its standard error will be biased downward. This means that the variance of the slope—the standard error squared—will tend to be understated and the inverse of the variance, used to determine the weight of the slope when pooled across studies, will tend to be overstated. The available studies do not include the correlations of RRs, which are usually adjusted for potential confounders; thus, the correlation of RRs, or their logarithms, cannot be calculated directly. A method outlined in Berlin et al. (*8*) and described fully by Greenland and Longnecker (*9*) adjusts for within-study correlation when the study observations (crude data) are available. This method was applied to studies that included crude data. In general, the effect of the adjustment was small.

The combined slope estimate for each country was obtained by weighting the estimate for each study inversely proportional to its variance. As an example, three U.S. studies could be corrected for within-study correlation (*10–12*), but the corrections had little impact on the combined estimate of the slope (0.0153 and 0.0149) and their standard errors (0.0042 and 0.0038), respectively. When the two uncorrected U.S. studies (*13,14*) were added, the combined slope estimate was reduced slightly to 0.0120 (standard error 0.0034). For

Table 1. Epidemiologic studies with data on intensity (cigarettes/day) of spousal smoking.

Study	Cases	Control[a]	Cigarettes/ day	Relative risk[b]	CI[c]	Regression slope	Weight (%)
China							
Du et al. (*28*)	28	53	0	1.00		0.0180	100.0
(case–control)	13	34	1–19	0.72	(0.32, 1.64)[d]		
	30	35	20+	1.62	(0.83, 3.15)		
Country estimate						0.0180	3.9
Greece							
Kalandidi et al. (*15*)	26	46	0	1.00		0.0111	68.2
(case–control)	34	39	1–20	1.54	(0.88, 2.70)		
	22	22	21–40	1.77	(0.93, 3.35)		
	8	9	41+	1.57	(0.64, 3.85)		
Trichopoulos et al. (*16*)[e]	24	109	0	1.00		0.0319	31.8
(case–control)	24	56	1–20	1.95	(1.13, 3.36)		
	14	25	21+	2.55	(1.31, 4.93)		
Country estimate						0.0178	12.2
Hong Kong							
Koo et al. (*29*)	32	67	0	1.00		0.0072	31.5
(case–control)	17	15	1–10	2.33	(0.9, 5.9)		
	25	35	11–20	1.74	(0.8, 3.8)		
	12	19	21+	1.19	(0.5, 3.0)		
Lam et al. (*30*)	84	183	0	1.00		0.0282	68.5
(case–control)	22	22	1–10	2.18	(1.14, 4.15)		
	56	66	11–20	1.85	(1.19, 2.87)		
	20	21	21+	2.07	(1.07, 4.03)		
Country estimate						0.0216	7.5
Japan							
Akiba et al. (*31*)	21	82	0	1.0		0.0173	33.7
(case–control)	29	90	1–19	1.3	(0.7, 2.3)[g]		
	22	54	20–29	1.5	(0.8, 2.8)[g]		
	12	23	30+	2.1	(0.7, 2.5)[g]		
Hirayama et al. (*32*)[h]	37	21,895	0	1.0		0.01897	66.3
(cohort)	99	44,184	1–19	1.41	(1.03, 1.94)		
	64	25,461	20+	1.93	(1.35, 2.74)		
Country estimate						0.0184	25.8
Scotland							
Hole et al. (*19*)[i]	1	491	0	1.00		0.0609	100.0
(cohort)	3	752	1–14	1.62	(0.17,15.68)		
	5	536	15+	4.55	(0.53, 39.00)		
Country estimate						0.0609	0.3
Sweden							
Pershagen et al. (*20*)	34	–	0	1.0		0.0325	100.0
(case–control)	26	–	1–15	1.0	(0.6, 1.8)		
	7	–	16+	3.2	(1.0, 9.5)		
Country estimate						0.0325	1.3
United States							
Cardenas et al. (*10*)	30	46,119	0	1.0		0.01135	31.0
(cohort)	9	11,458	1–19	1.1	(0.5, 2.2)		
	22	24,713	20–39	1.2	(0.7, 2.2)		
	13	9,858	40+	1.9	(1.0, 3.6)		
Garfinkel (*14*)[f]	65	–	0	1.00		0.0050	32.1
(cohort)	39	–	1–19	1.27	(0.85, 1.89)		
	49	–	20+	1.10	(0.77, 1.61)		
Garfinkel et al. (*11*)	44	157	0	1.00		0.0213	29.9
(case–control)	29	90	1–9	1.15	(1.1, 1.8)		
	17	56	10–19	1.08	(1.4, 2.7)		
	26	44	20+	2.11	(1.9, 4.1)		
Humble et al. (*13*)	–	–	0	1.0		0.0142	2.3
(case–control)	–	–	1–20	1.8	(0.6, 5.6)[g]		
	–	–	21+	1.2	(0.3, 5.2)[g]		
Kabat et al. (*12*)	26	71	0	1.00		0.0035	4.7
(case–control)	17	50	1–10	0.82	(0.42, 1.61)		
	12	28	11+	1.06	(0.49, 2.30)		
Country estimate						0.0120	49.1
Combined estimate (across countries): slope = 0.0157, standard error = 0.0022							

[a]Number of controls in case–control studies; number without lung cancer in cohort studies. [b]Odds ratio for case–control studies. Relative risk for cohort studies. [c]95% confidence interval unless indicated otherwise. [d]Estimated from raw data by Wolf's method. [e]Data from Trichopoulos et al. (*16*) with relative risks corrected [communication from Trichopoulos (*33*)]. [f]Values under "Relative risk" are mortality ratios of observed to expected lung cancer deaths. Values under "Cases" are numbers of observed lung cancer deaths. [g]90% confidence interval. [h]Standardized for age of subject [from Hirayama (*32*)]. Values under "Cases" are numbers of lung cancer deaths; values under "Controls" are total population. [i]Data submitted by author (Hole).

each country with more than one study, heterogeneity of slopes between studies was tested. The combined estimate served as the comparison from which squared differences were calculated for a chi-squared test, as shown in Greenland and Longnecker (*9*).

The weights used for combining study results within countries and the weights used to combine those results across countries are expressed as percentages in Table 1. For example, for Greece, the study by Kalandidi et al. (*15*) was weighted more heavily than the study by Trichopoulos et al. (*16*)— 68.2% compared to 31.8%—to obtain the country estimate for Greece. The resultant country estimate for Greece was weighted 12.2% when estimates were combined across countries to obtain the slope estimate of 0.0157 (standard error 0.0022) shown at the bottom of the table. The same chi-squared test applied to test for heterogeneity between studies within the same country was applied to test for heterogeneity between countries, using the combined estimate for all countries as the comparison.

An additional check on the prediction model for the United States, i.e., the meta-regression from studies within the United States, is conducted as follows. The excess risk is predicted at the average adult male smoking rate of 24 cigarettes/day. That value is then compared with meta-analytic results from other sources based on dichotomous data (i.e., where presence/absence of lung cancer in study participants is simply categorized by whether or not the husband smokes, not by how much he smokes). The U.S. model is used also to predict the RR from spousal smoking at the 95th percentile of adult male smoking rate. A downward adjustment of model-predicted RRs is made for bias from smoker misclassification, using the method of Wald and colleagues (*17*). The parameter values used with that method are marriage aggregation factor, 3.5; proportion of misclassified smokers, 7%; true relative risk of misclassified smokers, 4. An upward adjustment in RR is then calculated for ETS exposure of the referent group, using the method described in Appendix A.

The extrapolation of risk from nonsmoking women married to smokers to nonsmoking women occupationally exposed is based on the prediction model for the United States and the NHANES III data (*18*) on serum cotinine levels (used as a biomarker of ETS exposure). From this relationship between the number of cigarettes/day smoked by the husband and levels of cotinine, the prediction model can be applied to estimate risk from cotinine levels alone. Data on serum cotinine and on airborne nicotine collected by personal monitors are used in this way to estimate risk from ETS in the workplace.

The referent group at this point is nonsmoking women not married to smokers. (Some studies included unmarried nonsmoking women as controls.) Unlike spousal smoking, in which there is a concordance between the smoking status of husband and wife, no adjustment appears to be needed for smoker misclassification in assessing risk from ETS at work. The same adjustment is made for ETS exposure of the referent group, however, because the referent group is the same as for spousal smoking. Based on personal monitoring of nicotine, the 95th percentile for nicotine exposure at work exceeds the 95th percentile from exposure at home. The same model-based procedure described above, including adjustments for misclassification and ETS exposure of the referent group as applicable, is applied to compare excess risks at the 95th percentiles of exposure attributable to spousal smoking and to occupational exposure.

Results

Figure 1 shows the meta-regression for each country and for all countries combined. There is no evidence of within-country or between-country heterogeneity. The equal or higher slopes for Greece, Hong Kong, Japan, and China, relative to that for the United States, are consistent with the outcome of higher countrywide estimates from dichotomous data in the U.S. Environmental Protection Agency (U.S. EPA) report [(*1*) studies through Tier 3 in Table 5-17]. The model for all countries combined predicts an excess risk of 17% (95% confidence interval [CI] = 12, 22) per 10 cigarettes/day. This estimate is somewhat lower than the 23% found in Hackshaw et al. (*3*) but within their 95% CI (14, 32). The difference in outcomes probably results from the slightly different composition of studies that was used. Hackshaw and colleagues used four studies not included here (*4–7*), whereas two studies are used here that Hackshaw did not include (*19,20*). For the United States alone, the predicted excess risk per 10 cigarettes/day is 13% (95% CI = 5, 21). (It may be noted that risks have not been adjusted for smoker misclassification or for exposure of the referent group at this point.) The exposure–response relationship for the United States in Figure 1 appears plausible, if not conservatively low, compared to the results from other countries. There may be ethnic or cultural differences between the United States and some other countries that create real differences in exposure to ETS at home or at work, or in susceptibility to lung cancer. Thus, the model for the United States alone with slope 0.012 is used for extrapolation of risk from the home to the workplace.

It may be useful to examine the five studies for the United States a bit further for their relative influence (as indicated under the "weight (percent)" column in Table 1) and for some of their specific characteristics. The two cohort studies (*10,14*) and one of the three remaining case–control studies (*11*) account for 93% of the total weight; the two remaining case–control studies (*12,13*) account for only 4.7and 2.3%, respectively. None of the studies includes former smokers except for Humble et al. (*13*), which adjusts for them in the statistical analysis. Controls are reasonably comparable to cases in the case–control studies. In Garfinkel et al. (*11*), controls were from the same hospitals as cases and matched on age; in Kabat et al. (*12*), controls were matched to cases on age, sex, race, hospital, and year of interview; in Humble et al. (*13*), controls were randomly selected from telephone sampling and from Medicare participants and frequency-matched to cases (1.2 controls per case) by sex, ethnicity, and 10-year age category. All five studies attempted to restrict cases to primary lung cancer. All cases were diagnosed or confirmed by histology in two studies (*11,12*) and to varying degrees in the remaining three studies.

The exposure–response model from the combined U.S. studies,

$$lnRR = 0.012X \qquad [2]$$

where X is cigarettes/day smoked by the husband, allows prediction of RR across the range of X. The model in Equation 2 is first tested by predicting risk with X equal to the average number of cigarettes/day smoked by adult U.S. male smokers. In the two large Cancer Prevention Surveys (CPS-I and CPS-II) (*21,22*) conducted by the American Cancer Society, the average number of cigarettes smoked per day by male smokers was 22.4 and 25.4, respectively, which reflect smoking habits in the 1960s and 1980s (*23*). For 24 cigarettes/day, an approximate average, the predicted RR from Equation 2 is 1.33 (excess risk 33% [95% CI = 4, 56]). That value is reduced to 1.25 (excess risk 25% [95% CI = 3, 42]) to adjust for bias from some ever

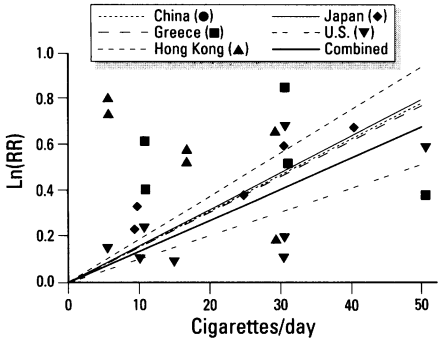

Figure 1. Natural logarithm of the relative risk of lung cancer for nonsmoking women married to smokers, as a function of the number of cigarettes smoked per day by their husbands.

smokers (former or current smokers) being incorrectly classified as nonsmokers.

The estimated RR of 1.25 may be compared with the values 1.19 (for meta-analysis of all U.S. studies with dichotomous data) and 1.28 (from the top-ranked study alone) published by the U.S. EPA (*1*). An extension of the U.S. EPA analysis that includes some subsequent studies (*24*) found an RR of 1.09 for all studies combined, and 1.30 for the two top-ranked studies combined. Both of those analyses included several studies not included in this article, as they did not contain exposure–response data; two of the five studies included here (*10,12*) were not published at the time of those analyses. The value 1.25 from the current method is well within the range of estimates from meta-analysis of data simply dichotomized on whether a woman's husband smokes.

The model may now be used to predict the upper and lower percentiles of excess lung cancer risk for a nonsmoking woman married to a smoker. As noted above, the model-predicted excess risk at the mean number of cigarettes/day smoked by males, after adjustment for smoker misclassification, is 25%. For male smokers between 30 and 70 years of age, the 95th percentile of the number of cigarettes smoked per day is 40 for CPS-I. The corresponding value for CPS-II differs slightly by age, with the 95th percentile at 40–50 cigarettes/day. A value of 45 cigarettes/day is used here as an approximate 95th percentile. Applying Equation 2 at that value, the estimated excess lung cancer risk at the 95th percentile exposure for a nonsmoking woman married to a smoker is 72% (95% CI = 27, 132). After adjusting for smoker misclassification, the excess risk is 67% (95% CI = 25, 123).

From the serum cotinine data of the NHANES III survey, as described and analyzed by Pirkle et al. (*25*), the mean difference in cotinine levels of persons exposed at home and those not exposed at home is 0.5576 ng/mL; among those who work, the mean difference between those exposed at work and those not exposed at work is 0.2343 ng/mL (see Appendix A). For serum cotinine as a biomarker of exposure to ETS, these figures suggest that for those exposed at work, the level of exposure at work is approximately 42% (0.2343/0.5576 = 0.42) of the level of exposure at home for those exposed at home.

Again, among nonsmoking women exposed to ETS at home (married or not), it is assumed that the excess risk attributable to the mean exposure at home, as determined by measures of serum cotinine, is equivalent to the excess risk from spousal smoking at the average rate of adult male smokers. The average rate of adult smokers is about 24 cigarettes/day, so for those women exposed to ETS at work, the average exposure from the workplace is roughly equivalent to the exposure from the home where the husband smokes about $0.42 \times 24 = 10$ cigarettes/day. From the exposure–response model in Equation 2, the estimated RR at 10 cigarettes/day is 1.13 (excess risk 13% [95% CI = 4, 21]). (It may be noted that the referent group is nonsmoking women married to nonsmokers).

There is a paucity of data on whether estimates of risk from ETS at work are biased from smoker misclassification and if so, what downward adjustment may be needed for correction. A bias would result if working misclassified smokers (typically former smokers or light current smokers who report themselves as lifelong nonsmokers) are more apt to be occupationally exposed to ETS than working women correctly reporting themselves as lifelong nonsmokers. In the absence of evidence to the contrary, there is assumed to be no bias from smoker misclassification for occupational exposure.

Occupational exposure to ETS varies considerably across workplace environments. Using personal monitors, Jenkins et al. (*26*) found that for most subjects, total exposure to nicotine or respirable suspended particles is higher in the home than in the workplace, for unrestricted smoking in either place. The 95th percentile for nicotine exposure at work, however, exceeds the 95th percentile for home exposure. Continuing to assume that home ETS exposure levels are proportional to cigarettes/day smoked by the spouse, the nicotine measurements in Jenkins et al. (*26*) are now used as a marker of ETS exposure because of lack of data on serum cotinine. The RR for the 95th percentile of exposure at work exceeds 1.72 (excess risk 72% [95% CI = 27, 132]), which is the prediction for spousal smoking at the 95th percentile of the number of cigarettes/day smoked by adult males prior to adjustment for smoker misclassification.

Individual studies of nonsmoking women married to smokers have typically adjusted their estimates of RR for some mix of confounders and risk modifiers but not for ETS exposure of the referent group (which arises because the referent group—nonsmoking women married to nonsmokers—is still exposed to some ETS from various sources). Discussion related to exposure of the referent group may be found elsewhere (*1,3,27*); the method used here is described in Appendix A. Based on comparison of urinary cotinine levels of nonsmoking women whose husbands smoke and those whose husbands do not smoke, an increase of about 11% is made to adjust for ETS exposure of the referent group, i.e., to make the risk relative to the risk from background (non-ETS) causes (see Appendix A).

Adjusting RRs upward by 11%, the predicted excess risk for a nonsmoking woman whose husband smokes 24 cigarettes/day is 39% (95% CI = 5, 65). At the 95th percentile of exposure, the adjusted excess risk is 85% (95% CI = 32, 156). Adjusting the excess risk at an average occupational level of ETS (assumed to be equivalent to exposure of a woman whose husband smokes 10 cigarettes/day) makes it 25% (95% CI = 8, 41). At the 95th percentile of occupational exposure, based on the nicotine data in Jenkins et al. (*26*), the adjusted excess risk is 91% (95% CI = 34, 167). The CI values are wide, contributing to uncertainty in comparisons. That observation notwithstanding, it appears that excess risk from ETS in the workplace is lower (by perhaps one-third) than that from spousal smoking at typical exposure levels. However, at the high end of exposure levels in both environments, the excess risk from occupational exposure is comparable to or higher than that from spousal exposure.

Discussion

Occupational exposure to ETS varies widely and is difficult to assess quantitatively aside from cotinine samples or from data collected on personal monitors. Current epidemiologic data on lung cancer and ETS exposure at work are largely from studies that have included questions about exposure to ETS at work in addition to that at home. A recent review and meta-analysis by Wells (*2*) found 14 studies that contained potentially useful data on lung cancer and exposure to ETS at work. The five studies that satisfy his selection criteria indicate a combined excess risk of 39% (95% CI = 15, 68), slightly above the 30% (95% CI = 9, 55) from the same five studies for women exposed to spousal smoking. At least five other meta-analyses have found no increased risk from occupational exposure, a discrepancy for which Wells offers an explanation. The estimates in Wells (*2*) and the current approach are reasonably close, considering the differences in data and methods.

The current approach indirectly brings data on spousal smoking to bear on the problem of estimating lung cancer risk from ETS in the workplace. There are several weaknesses, however, that should be clearly identified. It is assumed that the RR from spousal smoking is reasonably well described by Equation 1, i.e., that the expected value of ln(RR) is proportional to the number of cigarettes/day smoked by the spouse. Although this model seems to provide an adequate description of the exposure–response data, it is still an approximation. There might be other models that fit the data as well or better. Study characteristics not examined might also have some influence, e.g., study design (case–control/cohort) or year of publication.

Changes in smoking habits in recent years may reduce the reliability of current spousal smoking as an indicator of past ETS exposure. People are now more aware of the potential hazards of passive smoking and may smoke less or be more likely to smoke outdoors.

RR undoubtedly depends on duration as well as intensity of exposure to tobacco smoke, but no data are available where exposure jointly includes both intensity and duration. The measures of occupational exposure to ETS, such as urinary or serum cotinine and personal monitoring of nicotine, necessary to the current approach pertain only to exposure intensity. An implicit assumption is that the durations of ETS exposures from spousal exposure and from the workplace are comparable.

For practical purposes, nicotine from tobacco smoke is the only source of cotinine in body fluids. Although not ideal, cotinine is a widely accepted biomarker of recent ETS exposure in nonsmokers. But it is also important to recognize that nicotine and cotinine are only proxy markers for the active agents in ETS that elicit lung cancer. As described previously, the excess risk attributable to nonsmoking women (married or not) at the average serum cotinine level for those exposed to ETS at home is assumed to equal the excess risk from spousal smoking at the average adult male smokers' rate of about 24 cigarettes/day.

Dietary differences between nonsmokers exposed to ETS and those unexposed are possible confounders that have not been taken into account (*1,3*). The possibility arises from evidence that diets low in fruits and vegetables are associated with a higher risk of lung cancer and studies showing that smokers eat less of those foods than nonsmokers. A dietary effect would be difficult to assess, however, and even more difficult to quantify with any degree of confidence. The U.S. EPA report (*1*) concludes that "the actual data of ETS studies do not support the suspicion that diet introduces a systematic bias in the ETS results". Similarly, an investigation of eight epidemiologic studies that directly recorded data on diet "confirmed the negligible effect of dietary confounding" (*3*). Although it seems unlikely that diet is a confounder, at least of consequence, dietary self-assessments are notoriously inaccurate and this issue cannot be completely laid to rest.

Publication bias that results because positive studies, i.e., those finding a significant effect, are more apt to be published than negative studies cannot be entirely dismissed. There are reasons, however, why such bias seems unlikely. Potential for detrimental health effects from ETS has been of widespread interest in the last 10–20 years, and numerous negative studies have appeared in the literature. It appears unlikely that a manuscript on ETS would not be submitted for publication or be editorially refused simply because it did not find a significant health effect. Epidemiologic studies are typically costly and time consuming, and investigators have an interest in getting the outcome published. With methods of meta-analysis commonly applied to combine results across studies, it is realized that even a small study with little power to detect an effect by itself contributes to the total pool of evidence.

Conclusions

The current approach brings additional evidence to bear on assessing the risk of lung cancer from occupational exposure to ETS and leads to the conclusions below. Further study is needed to validate the assumptions and methods on which they are based. That notwithstanding, however, the current approach provides additional evidence of an increased risk of lung cancer in nonsmokers occupationally exposed to ETS. Tobacco smoke has been linked with heart disease as well as lung cancer and other maladies. Federal and numerous state agencies have restricted smoking in the workplace as a protective measure for employees. The large number of nonsmokers in the U.S. work force and the imperative to assure their occupational safety and health underscore the importance of further assessment and characterization of risks from ETS in the workplace.

- The application of data from studies of lung cancer and U.S. nonsmoking women married to smokers, in conjunction with data on serum cotinine levels and personal monitoring of nicotine, affirms an increased risk of lung cancer to nonsmokers from occupational exposure to ETS.
- The predicted increase in lung cancer risk for a nonsmoking woman exposed to ETS at work is 25% (95% CI = 8, 41) relative to the risk from background (non-ETS) sources. The excess risk predicted at the 95th percentile of occupational exposure is 91% (95% CI = 34, 107).
- The excess risk from ETS at work appears to be less (by perhaps one-third) than that from spousal smoking at typical exposure levels. At the high end of exposures, however, the excess risks appear to be comparable or higher than that from ETS at work.

Appendix A

Serum Cotinine

Pirkle et al. (*25*) analyzed data from NHANES III (*18*), a nationally representative cross-sectional survey that included measurements of serum cotinine, a metabolite of nicotine, on a large number of people. From Pirkle et al., Table 4 (*25*), the geometric mean cotinine levels (nanograms per milliliter), by source of reported ETS exposure, were as follows for working men and women at least 17 years of age: at both home and work (0.926), at home only (0.651), at work only (0.318), at neither home nor work (0.132). It is assumed that any gender differences in the mean values are negligible, so that these values are similar to what would be obtained for women only. For our purpose, estimates are needed of average serum cotinine levels in women with ETS exposure *a*) at home, *b*) not at home, *c*) at work, and *d*) not at work. From the data in Table 2 of Pirkle et al. (*25*) for women reporting no tobacco use and between the ages of 20 and 59, the following percentages are easily determined for sources of ETS exposure: at both home and work (6.46), at home only (14.45), at work only (19.75), and at neither home nor work (59.34). These percentages were used to obtain weighted-average cotinine levels for women exposed to ETS in locations *a–d* above. For example, for ETS exposure *a*) at home $(6.46 \times 0.926 + 14.45 \times 0.651)/(6.46 + 14.45) = 0.7360$. Similarly, the weighted means for the remaining categories are *b*) not at home, 0.1784; *c*) at work, 0.4679; and *d*) not at work, 0.2336.

Adjusting Relative Risk for the Exposure to the Referent Group

The referent group for the RR of nonsmoking women married to smokers is nonsmoking women married to nonsmokers. However, that referent group has some exposure to ETS, and hence some excess risk of lung cancer from it relative to the risk from non-ETS sources (referred to as background sources). To convert RR to be relative to background risk, RR is simply multiplied by the risk of the referent group relative to that of the background risk. The method described more fully in Hackshaw et al. (*3*) is implemented to calculate that multiple.

Let $1 + X$ denote the multiple, where X is the excess risk of the referent group relative to background risk. Then

$$RR = (1 + ZX)/(1 + X), \qquad [3]$$

where ZX is the excess risk of women with husbands who smoke relative to background risk, and $Z > RR > 1$. The solution for $1 + X$, for known Z and RR is

$$1 + X = (Z - 1)/(Z - RR). \qquad [4]$$

Using urinary cotinine as an index of uptake of ETS, the cotinine levels in women exposed to spousal smoking are about three times those without spousal exposure. Then assuming that the excess risk (relative to background) is approximately linear to uptake of ETS for this calculation, the value of Z in

Equation 3 is about three. To be consistent with the way Z was constructed, the value of RR at $Z = 3$ should be the risk of women married to smokers relative to that of women not married to smokers. As noted in the section of results, estimates of RR in the United States have varied from about 1.10 to 1.30. Over that range for RR, the solution to X in Equation 3 ranges from 0.05 to 0.18. The value of X corresponding to $RR = 1.20$, $X = 0.11$, is used in the current analysis. The corresponding multiple to adjust for ETS exposure of the referent group is then $1 + X = 1.11$.

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