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# Lung Cancer Risk and Workplace Exposure to Environmental Tobacco Smoke

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*Objectives.* We sought to quantitatively evaluate the association between workplace environmental tobacco smoke exposure and lung cancer.

*Methods.* We performed a meta-analysis in 2003 of data from 22 studies from multiple locations worldwide of workplace environmental tobacco smoke exposure and lung cancer risk. Estimates of relative risk from these studies were analyzed by fitting the data to fixed and mixed effects models. Analyses of highly exposed workers and of the relationship between duration of exposure and lung cancer were also performed.

*Results.* The meta-analysis indicated a 24% increase in lung cancer risk (relative risk [RR] = 1.24; 95% confidence interval [CI] = 1.18, 1.29) among workers exposed to environmental tobacco smoke. A 2-fold increased risk (RR = 2.01; 95% CI = 1.33, 2.60) was observed for workers classified as being highly exposed to environmental tobacco smoke. A strong relationship was observed between lung cancer and duration of exposure to environmental tobacco smoke.

*Conclusions.* The findings from this investigation provide the strongest evidence to date that exposure to environmental tobacco smoke in the workplace is associated with an increased risk of lung cancer. (*Am J Public Health.* 2007;97: XXX–XXX. doi:10.2105/AJPH.2004.061275)

Exposure to environmental tobacco smoke (ETS) has been recognized as a cause of human cancer by the US Surgeon General,[1] the National Institute for Occupational Safety and Health,[2] the US Environmental Protection Agency,[3] the California Environmental Protection Agency,[4] the National Health and Medical Research Council of Australia,[5] the Great Britain Department of Health,[6] and most recently, the International Agency for Research on Cancer.[7] Evidence for this association has come primarily from studies of nonsmokers who are married to a smoker, and meta-analyses of these studies have demonstrated strong and consistent evidence for an association.[3,8,9]

Demonstrating an association between workplace ETS exposure and lung cancer risk has been more difficult. Early meta-analyses failed to demonstrate an association between workplace ETS exposure and lung cancer risk among nonsmokers,[10–14] but a statistically significant association has been reported in the 3 most recently published meta-analyses.[15–17] We sought to extend the previous meta-analyses by including additional studies and by conducting analyses stratified by level of exposure, which was not performed in the previous meta-analyses.

## METHODS

Studies of lung cancer and workplace ETS exposure were identified from previously conducted workplace ETS meta-analyses[10–17] and from a MEDLINE and EMBASE literature review that was conducted January 1, 2003. A total of 22 studies with information on workplace exposure to ETS and lung cancer risk were identified.[16,18–38] Key design characteristics of the studies and the overall findings from these studies are presented in Table 1.

The most recent updates of the studies as of January 1, 2003, were used. Studies that were a part of larger, multisite studies were excluded. An exception to this was the study by Kreuzer et al.,[35] which had substantial overlap with the larger multicenter study by Boffetta et al.[19] M. K. provided us with the results from an analysis that included only the participants who were not in the study conducted by Boffetta et al.,[19] and these findings were included in our meta-analyses. Where possible, results adjusted for confounders (e.g., age, exposure to occupational carcinogens, or spousal exposure to ETS) were used, but in a few cases only unadjusted results were available. Reynolds et al.[27] was chosen over Fontham et al.[39] because the former study controlled for exposure to ETS from the spouse. Preference was given to the use of gender-specific results where available. Studies by Brownson et al.[40] and Butler[41] were excluded from the analysis because they included former smokers. A study by Stockwell et al.[42] was excluded because it provided no quantitative data, and a study by Janerich et al.[43] was excluded because it only reported results from a regression analysis that used units that were not compatible with other studies.

### Data Abstraction

Relative risk (RR) estimates, confidence intervals (CIs), and information on key study characteristics were coded for evaluation in the meta-regression analysis including: (1) whether the study findings were adjusted for potential confounding by age, diet, race, exposure to ETS from a spouse, or other occupational carcinogens; (2) whether the measure of ETS exposure only reflected recent jobs; (3) whether more than 50% of the participants were directly interviewed; (4) whether the study reported the counts of case and control participants stratified by ETS exposure; (5) whether the ETS exposures were likely to be greater than minimal; (6) whether there was significant exposure to other lung carcinogens (e.g., coal heating fumes in China); (7) whether the study included histopathologic confirmation of the cases; (8) the geographic area of the study (America, Europe, or Asia); (9) the gender of the study participants; and (10) the year of publication (before 1990, 1990–1999, or 2000 or later). These first 5 factors were used in the previous meta-analysis by Wells[15] as criteria for study

**TABLE 1—Key Study Design Features and Relative Risk (RR) and 95% Confidence Intervals (CI) for Lung Cancer in Never Smokers Exposed to Environmental Tobacco Smoke at the Workplace Compared With Never Smokers Who Were Not Exposed: Meta-analysis of Data From Multiple Locations Worldwide, 2003**

| Reference (Graph ID) | Location | Time Period | Gender | No. Cases | Covariate Adjustments[b] | Exposure Period | Histologic Confirmation | RR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Kabat et al.[18] (1f) | USA | 1971–1980 | women | 53 | none | current | no | 0.7 (0.3, 1.5)[c] |
| Kabat et al.[18] (1m) | USA | 1971–1980 | men | 25 | none | lifetime | no | 3.3 (1.0, 10.6)[c] |
| Koo et al.[19] (2) | Hong Kong | 1981–1983 | women | 88 | none | lifetime | yes | 1.2 (0.5, 3.0)[c] |
| Garfinkel et al.[20] (3) | USA | 1971–1981 | women | 76 | a | lifetime | yes | 0.9 (0.7, 1.2) |
| Wu et al.[21] (4) | Los Angeles | 1981–1982 | women | 29 | a | lifetime | no | 1.3 (0.5, 3.3)[d] |
| Lee et al.[22] (5f) | England | 1979–1982 | women | 15 | none | NR | no | 0.6 (0.2, 2.3)[c] |
| Lee et al.[22] (5m) | England | 1979–1982 | men | 10 | none | NR | no | 1.6 (0.4, 6.6)[c] |
| Shimizu et al.[23] (6) | Japan | 1982–1985 | women | 90 | a | current | yes | 1.2 (0.6, 2.6)[c,e] |
| Kalandidi et al.[24] (7) | Greece | 1987–1989 | women | 89 | none | lifetime | no | 1.4 (0.8, 2.5)[c] |
| Wu-Williams[25] (8) | China | 1985–1987 | women | 415 | a | lifetime | no | 1.2 (0.9, 1.6)[g] |
| Kabat et al.[26] (9f) | USA | 1983–1990 | women | 58 | a | lifetime | yes | 1.2 (0.6, 2.1) |
| Kabat et al.[26] (9m) | USA | 1983–1990 | men | 41 | a | lifetime | yes | 1.0 (0.5, 2.1) |
| Reynolds et al.[27] (10) | USA | 1986–1990 | women | 528 | a,d,s,r,o | lifetime | yes | 1.6 (1.2, 2.0) |
| Schwartz et al.[28] (11) | USA | 1984–1987 | both | 257 | a,r | NR | no | 1.5 (1.0, 2.2) |
| Sun et al.[29] (12) | China | NR | women | 230 | a | NR | yes | 1.4 (0.9, 2.0) |
| Wang et al.[30] (13) | China | 1992–1994 | women | 135 | none | NR | no | 0.9 (0.5, 1.8) |
| Boffetta et al.[31] (14) | Europe | 1988–1994 | both | 650 | a | lifetime | no | 1.2 (0.9, 1.5) |
| Boffetta et al.[32] (15) | Europe | 1994–1996 | both | 70 | a | lifetime | no | 1.5 (0.8, 3.0)[d] |
| Zaridze et al.[33] (16) | Russia | NR | women | 189 | a | current | yes | 0.9 (0.6, 1.4) |
| Rapiti et al.[34] (17) | India | 1991–1992 | both | 58 | a | lifetime | yes | 1.1 (0.3, 4.1) |
| Zhong et al.[16] (18) | China | 1992–1994 | women | 504 | a | lifetime | no | 1.7 (1.3, 2.3) |
| Kreuzer et al.[35] (19)[f] | Germany | 1990–1996 | both | 123 | a,r | lifetime | yes | 1.1 (0.7, 1.7) |
| Lee et al.[36] (20) | Taiwan | 1992–1998 | women | 268 | a,o | lifetime | yes | 1.5 (0.5, 2.4) |
| Wang et al.[37] (21) | China | 1994–1998 | both | 233 | a | lifetime | no | 1.6 (0.7, 3.3) |
| Johnson et al.[38] (22) | Canada | 1994–1997 | women | 71 | none | lifetime | yes | 1.3 (0.4, 4.0) |

*Note.* NR = not reported.
[a]Graph ID refers to the symbol used in plotting the studies in Figures 1–3.
[b]Covariates that were adjusted for in the analysis: a = age; r = race; d = diet; s = exposure to environmental tobacco smoke from spouse; and o = occupational exposure to other carcinogens.
[c]We estimated the paper on the basis of the results presented in the article in which the results appear.
[d]Results are for adenocarcinoma of lung only.
[e]The 95% CI was not reported. It was estimated with the average standard error taken from Kalandidi et al.[24] and Nyberg et al.,[53] because all 3 studies had similar numbers of lung cancer cases.
[f]Some of the cases and controls in Kreuzer et al.[35] were part of another study included in this table (Boffetta et al.[31]). The results given here are based on those cases and controls that were not part of the Boffetta study (M. K., written communication).
[g]The reported result was 1.1 (95% CI = 0.9, 1.6); the authors reported the correct estimates in Wells.[15]

selection. We examined the influence of these 5 factors plus the additional 5 factors listed here on the results in our meta-regression analysis. Consistent with Wells,[15] we excluded studies that included active or former smokers.

## Meta-regression

Both fixed and mixed-effects linear models were fitted to the natural logarithm of the RRs reported in the studies using the Proc Mixed procedure of SAS (SAS Institute Inc, Cary, NC). The variances, which were derived from the CIs reported in the studies, were used to specify the residual variances in our models.[44] The heterogeneity of the studies was assessed by calculating a likelihood ratio test of the variance parameter that corresponded to the addition of a random effect for each study, and by the test given by DerSimonian and Laird.[45]

Meta-regression analyses were also conducted to evaluate exposure–response analyses results. This effort was limited by the fact that not all of the studies included such information, and those that did frequently used different measures of exposure. The only measure that was defined in a consistent fashion in several studies was duration of exposure, which was reported in 6 of the studies. The midpoints of the exposure categories were used in the regression, except for the last categories, which were open-ended. For the open-ended categories, we multiplied the cutpoint by 1.5 (up to a maximum of 45 years) and used this value in the regression. Because the regression included several points from the same study, we used a

**TABLE 2—Relative Risk (RR) and 95% Confidence Interval (CI) Results for Highest Cumulative or Intensity of Exposure Groups: Meta-analysis of Data From Multiple Locations Worldwide, 2003**

| Reference | Gender | Exposure Measure[a] | RR (95% CI) |
|---|---|---|---|
| Boffetta et al.[31] | both | ≥89 level×hours per day×years[b] | 2.07 (1.33, 3.21) |
| Johnson et al.[38] | women | ≥64 smokers×years | 1.58 (0.6, 4.0) |
| Kabat et al.[18] | men | Smokers×hours per week×years[c] | 1.21 (0.47, 3.13) |
| Kabat et al.[18] | women | Smokers×hours per week×years[c] | 1.35 (0.64, 2.84) |
| Kalandidi et al.[24] | women | Duration×number coworkers[d] | 1.08 (0.24, 4.87) |
| Kreuzer et al.[35] | both | >100.6 level×hours per day×years[b] | 2.64 (1.07, 6.54)[e] |
| Lee et al.[36] | men | Average to a lot | 0.46 (0.05, 4.65)[f] |
| Zhong et al.[15] | women | ≥4 coworkers smoked | 3.0 (1.8, 4.9) |
| Meta-analysis | | | |
| Fixed effects | | | 2.01 (1.55, 2.60) |
| Mixed effects | | | 2.01 (1.33, 2.60) |

[a]The measure of exposure used to categorize workers varied from study to study. For studies that presented more than 1 measure, preference was given to exposure measures that reflected both intensity and duration (i.e., cumulative exposures).
[b]The total number of years of exposure weighted for the number of hours of exposure per day and for a subjective index of level of smokiness at the workplace (1 = very smoky, 0.5 = fairly smoky, and 0.2 = a little smoky).
[c]The highest tertile of exposure was compared with the lowest tertile. The actual values of the tertiles were not presented in the article.
[d]The results are for a comparison between the highest and lowest quartiles of "the time-weighted sum of exposure at work, the exposure being based on the number of smokers among people working in the same closed space." The units of these quartiles are not presented in the article.
[e]Results are from an analysis that excluded cases and controls that were in the analysis by Boffetta et al., 1999, which was not presented in the original analysis.
[f]Crude results not adjusted for any risk factors.

methodology that accounted for the correlation between the points.[46]

Seven studies reported exposure–response findings with categories that were based on cumulative exposure or intensity of exposure. As shown in Table 2, the definition of these measures varied from study to study. Unlike with duration of exposure, the results for intensity of exposure could not be analyzed as a continuous variable in a regression model. We performed a meta-analysis that combined the results from the highest exposure group in each study. For studies that reported the results for more than 1 exposure measure, we used cumulative exposure rather than intensity of exposure.

### Sensitivity and Influence Analyses

We performed a sensitivity analysis in which we varied the assumed duration of exposure for the last category in the duration of exposure–response analysis using values of the cutpoint or assuming 45 years of exposure. We evaluated the influence of individual studies by performing analyses in which we dropped 1 study at a time.

### Evaluation of Publication Bias

Publication bias is a common concern in meta-analysis that is related to the tendency of journals to favor the publication of large and positive studies. We chose a commonly used method for detecting publication bias, which is a graphical plot of estimates of the RRs from the individual studies versus the inverse of their variances, which is commonly referred to as a "funnel plot." An asymmetry in the funnel would be expected if there was publication bias with smaller studies tending to show larger RRs, because small studies with statistically nonsignificant results would be less likely to be reported.[47]

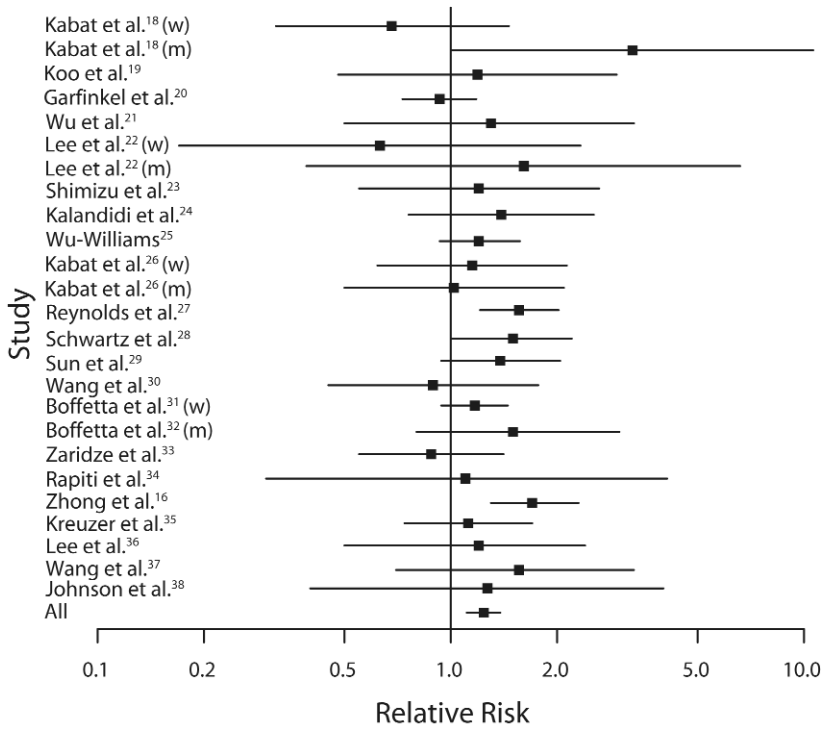
## RESULTS

The overall results from the individual studies are displayed in Table 1 and Figure 1. Twenty of the 25 RR estimates were greater than 1 indicating an excess lung cancer risk among nonsmokers exposed to ETS at the workplace. The meta-analysis RR from the fixed model was 1.24 (95% CI=1.18, 1.29). The RR estimate was virtually unchanged in the mixed-effects model, but the 95% CI was slightly wider (1.17, 1.31). There was no statistically significant evidence of heterogeneity based either on testing the variance of the random effects ($P$=.08) or using the DerSimonian–Laird test ($P$=.49). The only design variable found to be a statistically significant predictor of risk (F=13.58; $P$<.01) was whether the study controlled for exposures to other occupational carcinogens. The coefficient for this variable indicated that the studies that controlled for this variable had a higher RR (1.59) than those that did not (1.14).

### Exposure–Response Analyses

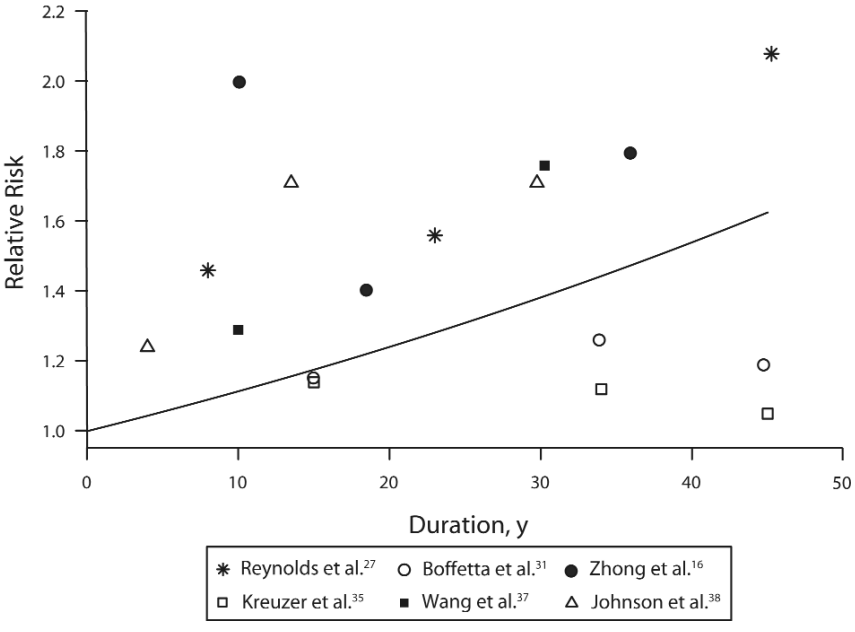
The results from the highest exposure categories in the studies and the meta-analysis of those findings are presented in Table 2. All but 1 of the RRs were elevated, and 3 of them were statistically significant. The meta-analysis RR from the fixed effects model was 2.01 (95% CI=1.55, 2.60; $P$<.001). The RR estimate was the same as that obtained from the random effects model, although the confidence interval was somewhat wider (95% CI=1.33, 2.60; $P$=.005). (Fitting a model with the Proc Mixed procedure resulted in a 0 estimate of the variance for random effects and thus, the fixed and random effects models produced identical results for the effect of high exposure. However, because we believe there should be a random effect in this case, we derived a CI from the random effects model with a profile likelihood method. The profile likelihood 95% CI is the set of all values that would not be rejected by a likelihood ratio test at the 5% level of significance.) The test for heterogeneity was statistically nonsignificant based on either testing the variance for random effects ($P$>.99) or the DerSimonian–Laird statistic ($P$=.37). None of the individual study design variables were found to be a statistically significant predictor.

The results for duration of exposure and a line from a meta-regression of these data are presented in Figure 2. The linear regression parameter for duration of exposure was highly statistically significant ($P$<.001), and there was




*Note.* The horizontal scale is displayed on a common logarithmic scale.

**FIGURE 1—Relative risks (with 95% confidence intervals) for a meta-analysis of individual studies from multiple locations worldwide: 2003.**




*Note.* The line in the plot is the fitted fixed model effect of duration.

**FIGURE 2—Relative risks plotted against duration of exposure in 2003 meta-analysis.**

virtually no evidence of statistical heterogeneity in this analysis ($P$=.42). Based on the slope (β) and standard error (SE) from the linear model (β=0.011; SE=0.0025), it is estimated that 45 years of exposure to ETS would be associated with an RR of 1.63 (95% CI=1.45, 1.82). (Forty-five years of exposure is often used by the Occupational Safety and Health Administration for estimating risks and for setting standards that are protective for workers exposed to a hazard for a "working lifetime.")

### Sensitivity and Influence Analysis

The effect of dropping 1 data point at a time from the analysis did not have a large effect on the magnitude of the overall results (estimated RR ranged from 1.18 to 1.27), or on the high exposure (estimate RR ranged from 1.73 to 2.12), or on the slope of the duration of exposure–response (β ranged from 0.009 to 0.014 and SE varied from 0.009 to 0.014). Dropping the studies that were excluded by Wells[15] slightly strengthened the results (RR=1.31; 95% CI=1.24, 1.38). Varying the assumption of the value for the last open-ended category from the cutpoint to 45 years had little influence on the regression coefficient (varied from 0.010 to 0.012) in the duration of exposure analysis.

### Evaluation of Publication Bias

The funnel plot of the log RRs versus the inverse of their variances of the individual studies is displayed in Figure 3. The plot formed a very distinct funnel shape with the log RRs evenly distributed around the meta-analysis RR regardless of the study variance. Therefore, there was no indication of an asymmetry in the study findings by the variance or size of the studies and, thus, little evidence for publication bias.

## DISCUSSION

Several organizations have concluded that there is a causal association between exposure to ETS from various settings and lung cancer.[1–7] The strongest support for this conclusion has come from studies that have examined exposure to ETS from a smoking spouse. The magnitude of the risk associated with exposures in the workplace has been less clearly established. The findings from this

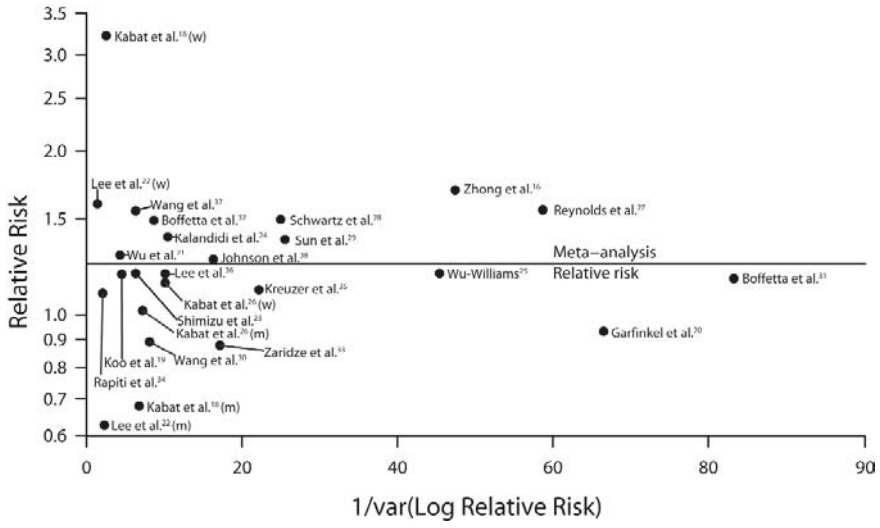



**FIGURE 3—Funnel plot of relative risks (on a log scale) versus the inverse of the variance of the log relative risks for studies included in the 2003 meta-analysis.**

investigation provide the strongest evidence to date that exposure to ETS in the workplace is associated with an increased risk of lung cancer. Although the overall meta-analysis findings suggest that this increased RR is modest (20%), the results from the analysis of highly exposed workers indicate a stronger effect with approximately a 2-times greater increase in risk.

Even if the lung cancer risk was elevated by only 20%, this would still constitute a significant public health concern because of the large numbers of workers potentially exposed. Although great strides have been made in limiting smoking in the workplace, the most recent estimates are that smoking is still permitted in approximately 30% of workplaces in the United States.[48]

Our results agree reasonably well with the findings from the most recently reported meta-analyses.[16–17] Our summary RR estimate (RR=1.24) was slightly higher than that reported by Zhong et al.[16] (RR=1.16) and Boffetta[17] (RR=1.17). These small differences may be attributable to our addition of several new studies that were not included in these previous meta-analyses. Our findings were somewhat lower than those reported by Wells[15] (RR=1.39) but were similar (RR=1.31) when we excluded the same studies as Wells. Our findings are inconsistent with largely negative results reported in several earlier meta-analyses.[10–14] The evidence for an association has clearly been strengthened by the inclusion of the more recent investigations that are generally of larger size and higher quality.

The evidence for a causal interpretation of our findings is greatly strengthened by our observation of a strong relationship among highly exposed workers and a statistically significant duration of the exposure–response relationship. It must be recognized that the exposure information from the available studies was very limited and of variable quality. Mean durations of exposures were not available from the studies and were estimated with the reported cutpoints of the categories. This undoubtedly resulted in some misclassification of exposure, which most likely weakened the slope for the exposure–response relationship.[49] Misclassification of exposure is also likely because in most studies a substantial proportion of the interviews were from next of kin, who are unlikely to have accurate knowledge of the subject's history of workplace exposure to ETS. Finally, misclassification of exposure is a concern because duration of exposure is often a poor measure of exposure in occupational studies because it does not reflect variations in exposure intensity by job or over time.

Measurements of ETS that used markers such as nicotine have demonstrated the high degree of variability between jobs, and even within jobs, on a day-to-day basis.[50] The large degree of variability in ETS exposures found in the workplace implies that there is a substantial dilution in the estimates of risk in the existing epidemiological studies that have used broad definitions of exposure from a wide variety of occupational settings. Our analysis of "highly" exposed workers was an attempt to overcome this dilution by focusing the analysis on individuals with substantial exposures.

Misclassification of disease is also a concern in this investigation. Histologic confirmation of lung cancer cases was conducted in approximately half of the studies, and the vast majority (18 of 22) of the studies included in this meta-analysis combined all histologic types of lung cancer. Two of the 22 studies included cases of adenocarcinoma only.[21,32] Mainstream cigarette smoking appears to be a stronger risk factor for squamous cell carcinoma and small cell carcinoma than for adenocarcinoma although all histologic forms appear to be associated with smoking.[51,52]

There is limited evidence to suggest that this may also be the case for ETS exposure. In the study by Boffetta et al.[31] it was reported that the association between workplace ETS and squamous cell carcinoma was stronger than for either adenocarcinoma or small cell carcinoma. In the paper by Zhong et al.[16] it was reported that the association with workplace ETS was stronger for non-adenocarcinomas than for adenocarcinomas. Hackshaw et al.[8] found in their meta-analysis a somewhat stronger relationship between ETS exposure from a spouse and squamous and small cell carcinoma (pooled RR=1.58) than with adenocarcinoma (pooled RR=1.25). Thus, it appears that including adenocarcinomas in this analysis may have diluted the overall association and that a stronger association might be apparent if the analysis could be limited to non-adenocarcinomas. Of particular concern is the inclusion in our analysis of the 2 studies that included only adenocarcinomas. However, these studies had odds ratios (ORs; Boffetta et al.,[32] OR=1.5; Wu et al.,[21] OR=1.3) that were very close to the meta-analysis result (RR=1.31), and thus, exclusion of these studies had little effect on our findings.

An additional concern in conducting this and most meta-analyses of epidemiological studies is that the studies differ with respect to what other risk factors they controlled for in their analyses. Most studies adjusted for age (n=16), 2 controlled for race, and 3 controlled for occupational exposures to lung carcinogens. One study controlled for a relatively large number of potential risk factors (age, race, occupation, diet, and spousal exposure to ETS).[20] Six studies presented unadjusted (crude) findings. One approach to dealing with this problem would be to estimate unadjusted effect measures for all of the studies and to use these crude estimates in the meta-analysis. This was in fact the approach taken in 1 of the previous meta-analyses for ETS.[8]

We rejected this approach because we believe that although consistency is desirable it should not be achieved at the expense of introducing potential bias into the analysis. However, we recognize that combining studies with different levels of adjustment for confounding may have introduced bias into our findings. The use of results from studies that control for variables that are not true confounders but are associated with exposure might tend to mask an association. The use of results from studies that fail to control for true confounders could bias our findings in either direction.

To evaluate the impact of combining studies with different levels of control of confounding we performed a sensitivity analysis in which we dropped the 6 studies with crude estimates of effect. The results from this analysis (OR=1.25; 95% CI=1.13, 1.38) were quite similar to the results from the analysis that included all of the studies (OR=1.24; 95% CI=1.18, 1.29). As described earlier, dropping the study that controlled for multiple risk factors[27] or any of the individual studies was not found to have a large effect on the study findings.

There is evidence to suggest that our findings may have been biased toward not observing an association by the lack of control of potential confounders in some studies. Only 1 of the studies controlled for spousal exposure, and the results for workplace ETS increased with control for spousal exposure.[27] Control for occupational exposures was found to be a significant predictor in our meta-regression analysis, and the studies that controlled for occupational exposures had a higher RR than studies that did not. Thus, it does not appear likely that the different levels of adjustment for confounders used in the studies had a large impact on our findings, and, if anything, there is some evidence to suggest that our findings may have been biased toward the null.

That there was virtually no evidence for heterogeneity in any of the analyses performed we performed was surprising. One might expect some degree of heterogeneity given differences in the study designs and the high degree of variability in the magnitude and duration of exposures in the populations studied. This was particularly surprising in our meta-analysis of the "highest" exposure groups, because in some studies this was based on cumulative exposure and in others it was based on intensity. The lack of heterogeneity may in part reflect the fact that these tests are not very powerful and that our sample size was small.

Publication bias is a serious concern with this, and all other meta-analyses, but our funnel plot analysis provided no evidence for this concern. Although it still is possible that some negative studies might not have been published around the time that the first studies were published (early 1980s), it seems unlikely that even small negative studies would not have been published subsequent to these initial reports given the large public interest in this issue. Furthermore, the strength of the evidence for the association appears to have become stronger rather than weaker with the publication of the more recent and higher-quality studies (e.g., Boffetta et al.[31] and Reynolds et al.[27]). This is not the pattern that one would expect if publication bias was a problem. The issue of publication bias may be a more serious concern for our duration of exposure and high-exposure analyses that were based on a subset of the studies that had this information. It is possible that studies that did not present this information had negative results; however, this seems unlikely given the importance of such analyses.

The meta-analyses may also have been biased if some of the study participants were truly ever smokers. The magnitude and direction of this bias would be difficult to predict, because it is unclear whether it would be correlated with the potential for workplace exposure to ETS. Misclassification of never smoking has been found to be a small source of bias in studies of exposure to ETS from a spouse.[8] Finally, all of the studies included in this analysis were case–control studies, and the possibility of recall bias cannot be fully discounted. Recall bias is related to the fact that people with lung cancer may be more prone to recall their ETS exposures than those without lung cancer. It seems unlikely that any of the aforementioned biases could fully explain our findings, particularly from the analyses of the highest exposure group and the positive relationship observed between duration of exposure and lung cancer.

The findings from this meta-analysis in conjunction with the findings from ETS studies of nonsmoking spouses provide compelling evidence that exposure to ETS in the workplace is a significant risk factor for lung cancer. We believe our results provide strong support for prior recommendations made by the National Institute for Occupational Safety and Health[2] and the current efforts by many communities for severely restricting smoking in the workplace. ■

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**Note.** *The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.*

## Contributors

This study was originated by L. Stayner, K. Straif, A.J. Sasco, K. Steenland, and M. Kreuzer. L. Stayner oversaw all aspects of the data collection, analysis, and writing of the article. J. Bena and R. Smith provided statistical support for the analysis. All authors were involved in interpreting the findings and reviewing drafts of the article.

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## Institutional Review Board

No clearance was necessary for the protection of human subjects because this was a quantitative review of the literature.

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