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Why EPA should not have classified

ETS as a group A carcinogen

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1. Introduction

Having recently received a copy of the final version of the EPA report "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders", and having had a chance to read the sections relevant to lung cancer, which conclude that "ETS is a human lung carcinogen, responsible for approximately 3,000 lung cancer deaths annually in the U.S. nonsmokers", this note summarizes the main reasons why I believe that the EPA's conclusion was incorrect. It also makes some other critical comments on the sections of the report relating to lung cancer.

Before giving my reasons and comments it should be noted that the report had undergone two previous drafts, for both of which I provided detailed written comments and made an oral presentation of key points. Virtually all of the points I make here have been made in these comments and presentations, and the EPA have chosen to ignore them despite their scientific validity. Others too made comments that were ignored, it being particularly notable that the final version - which is really very similar to the second draft - has even failed to take into account many important points made by their own Scientific Advisory Board. The Public Meeting in July

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1992 where outside scientists, and the Scientific Advisory Board, gave detailed comments clearly served virtually no purpose, since the EPA chose to ignore nearly all the points made.

2. Failure to consider workplace and childhood exposure to ETS

In attempting to evaluate whether an association with ETS exposure exists, it is clearly important to consider all indices of exposure that provide adequate data for analysis. Although in 1986 it was true that smoking by the spouse was the only index of exposure for which any worthwhile amount of data existed, this is clearly not the case today. There is by now a substantial body of information relating to workplace exposure and to childhood exposure from the parents. The EPA report attempts to justify restriction to spousal exposure on the basis that there is more data on this index - so there is, but not far more as they claim. Tables 1-3 summarize the relevant data for the three indices, and it can be seen that although there is an association of lung cancer with spousal exposure, there is no association whatsoever between lung cancer and either workplace or childhood exposure. Furthermore the confidence limits of the three estimates are similarly narrow, indicating similar precision of the estimates.

As I shall show below, there are particular problems of bias from misclassification and from confounding associated with use of spousal smoking as an index. Given one has one index known to be subject to bias which produces a positive association, and two other indices apparently not so subject to bias and which produce no

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association, this strongly suggests the possibility that the positive association may be spurious. This suggestion does not emerge from the EPA report simply because it chooses to keep concealed from the reader the very existence of the overall evidence from childhood and workplace exposure showing no association. While one might argue that classifying subjects by spousal exposure is a more sensitive way of separating those with higher and lower ETS exposure than is classifying subjects by workplace exposure, lack of association of workplace exposure with lung cancer hardly fits in well with EPA's implicit assumption (via use of Cummings' "Z-ratio" of 1.75 - see also section 11) that more than half of total ETS exposure comes from sources other than the spouse.

The EPA derived estimates of risk per unit of exposure based on epidemiological evidence relating to spousal smoking, and used these estimates indirectly to compute risk resulting from workplace and other non-spousal exposure. Had they used estimates of risk per unit of exposure based on evidence relating to workplace smoking, and used these estimates indirectly to compute risk resulting from spousal and other non-workplace exposure, they would have got an overall risk estimate that was very different, and close to zero. While the latter approach is not correct, the former is also not. It is clear that any evaluation should have taken into account all the evidence, and that EPA's approach has resulted in upward bias of the estimated risk.

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3. Failure to take into account properly the possibility of confounding

Non-smokers married to smokers may have a higher risk of lung cancer than non-smokers not married to smokers because they have a higher exposure to risk factors for lung cancer other than ETS. This possibility of confounding by other risk factors is considered in the EPA report in section 5.4, and it is concluded that none of the risk factors studied (history of lung disease, family history of lung disease, heat sources for cooking or heating, cooking with oil, occupation, and diet) explains the association between lung cancer and ETS exposure.

There are three basic logical flaws in the EPA's argument. First, they appear to require one risk factor to explain the whole of the observed relative risk in relation to spousal exposure. This is clearly far too stringent a requirement. Bias might arise from many sources, of which confounding is only one. Confounding might arise from many risk factors of which the one under consideration is the only one. Part of the observed increase in relative risk may be a result of chance.

Secondly, when trying to determine whether a factor actually elevates lung cancer risk, they virtually restrict their attention to evidence collected in the ETS/lung cancer studies themselves, when there is abundant relevant data from other sources. There is a vast literature indicating that workers in various occupations have an increased risk of lung cancer not explained by smoking. There is also a vast literature showing reduced consumption of various

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dietary components such as beta-carotene, fruit, and vegetables to be associated with an increased risk of lung cancer, and a recent paper by Candelora et al (1992) has confirmed this is as true for non-smokers as it is for smokers. There is also a lesser literature indicating increased dietary fat is a risk factor. Eleven studies (Lee, 1993, in press) have demonstrated an approximate doubling of lung cancer risk in relation to family history of lung cancer.

Thirdly, there is also growing evidence that ETS exposure is associated with increased exposure to diet and other risk factors. Some early evidence is summarized in my Karger book (Lee, 1992). More recent and important evidence comes from analysis of the large Health and Lifestyle Survey which I conducted with my colleagues Alison Thornton and John Fry - see Annex A, an earlier draft of which went to EPA but was not taken into account. In this analysis prevalence of 33 risk factors, many relevant to lung cancer, were compared in smokers, ex-smokers, passive smokers (non-smokers who lived with a smoker) and an unexposed group (non-smokers who did not live with a smoker). Compared with the unexposed group, smokers of 20+ cigarettes a day had a highly significantly increased prevalence of 27 of these factors and a significantly decreased prevalence in only two. The prevalence of many of these risk factors showed a dose-related increase with amount smoked, a time-related decrease with time since giving up smoking, and an increase in passive smokers. The increases in prevalence of many risk factors among passive smokers was sufficient to cause moderate bias, and

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confounding clearly could have been an important contributor to the increased risk of lung cancer seen in relation to ETS exposure in Table 3 of this note.

The EPA report also does not make it clear that some studies of ETS and lung cancer have not even properly adjusted for age. Also many studies have failed to exclude unmarried subjects, so that the key comparison of non-smokers married to a smoker (who are by definition all married) and non-smokers married to a non-smoker (a mixture of married and unmarried individuals) automatically confuses effects of ETS exposure and effects of marital status (and its correlates) on lung cancer risk. For details of the studies in question, see Table 3.27 of Lee (1992a).

4. Failure to correct fully for bias due to misclassification of active smoking status

The EPA report uses the methodology of Judson Wells to correct for bias due to misclassification of active smoking status. The mathematical method, described in Appendix B of the report, is very difficult to follow, a point made on the second draft by numerous members of the Scientific Advisory Board and other commenters, but essentially ignored by EPA who chose to publish only a minimally revised version. It is also mathematically incorrect to some extent, for detailed reasons I have explained in my submission (available on request). More important, Wells underestimates the extent of misclassification in Western populations in his calculations and assumes, without any justification, that misclassification rates in

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Asian populations are of a similar magnitude to those in Western populations. In Annex B, a letter shortly to appear in Environment International, I present detailed data justifying a figure of 2.5% in Western populations for the rate at which typical ever smokers are misclassified as never smokers. Applying this rate, assuming a concordance ratio of 3.0 (justified in Lee 1992a), and using techniques as described in Lee (1991), I demonstrate in Annex B that this level of misclassification has a marked effect on the spouse smoking relative risk estimate for the US data, essentially eliminating the association. Table 3 of this report shows the effect of the adjustment study by study.

Annex C is a copy of a paper recently submitted to the Lancet by Yano and Yanaka describing a study of 400 Japanese women who answered questions on smoking habits, exposure to ETS, diet and lifestyle factors, and supplied urine for cotinine analysis. One of the major conclusions of this report is that over 30% of women who were in fact smokers claimed to be non-smokers. The existence of such a high misclassification rate, far higher than in the West, implies that the misclassification corrections applied by EPA/Wells to Japanese (and perhaps other Asian data) are totally inadequate.

There is little doubt that the EPA have severely under-corrected for bias due to misclassification of active smoking status.

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5. Using a dubious assumption that in Japanese populations marriage to a smoker involves increased exposure to ETS

A second striking result in the paper by Yano and Yanaka is that, after eliminating misclassified smokers, there was no evidence that non-smokers married to smokers had higher average cotinine levels than non-smokers married to a non-smoker. In fact in this study cotinine was non-significantly lower in the former group. A recent personal communication by Jarvis indicates that this may not be a freak result at all. In a study of Japanese schoolchildren he found that cotinine was increased if the mother smoked but not if the father smoked. Both studies in Japan seem to suggest that the father, if he smokes, does not do so at home to any great extent. If this is so it would inevitably suggest that elevated risks of lung cancer in Japanese non-smoking women in relation to marriage to a smoker reported in some studies were not a result of ETS exposure.

6. Failure to consider histological type

The multiplication of risk of lung cancer in relation to active smoking is much greater for squamous-cell cancer than for adenocarcinoma. If, as the EPA assume, ETS is merely a reduced dose of active smoking, one would expect to see effects, if any, for squamous-cell cancer. In fact, as discussed in Lee (1992a), the evidence is conflicting regarding the histological type of lung cancer where the association is strongest. A major weakness of the EPA report is that it makes no attempt to compare and contrast results for these two major types of lung cancer. They do not use



the normal scientific process of using all available methods of testing their hypothesis. Consistency is a criterion that is cited for testing causality, but EPA do not actually test for consistency here or in other areas.

7. Failure to test for effects of study weaknesses

The EPA has conducted an exercise classifying studies as weak or strong according to various criteria, and into tiers of studies according to usefulness for testing the hypothesis that ETS causes lung cancer. Surprisingly, however, they did not compare relative risk estimates of studies, weak or strong, according to specific criteria. In my book (Lee, 1992a) I point out that one can separate studies that show or do not show a major lack of comparability between cases and controls in the circumstances in which data were collected, and that the observed relative risk is significantly higher in the studies showing such a failure to compare like with like. This casts doubt on the validity of meta-analyses involving all the studies, good and bad alike, and suggests the overall estimate is biased upward by the bad studies, but EPA do not attempt such analysis.

8. Failure to address publication bias

It is well known that any meta-analysis should consider the possibilities of bias due to failure to publish null studies. My book (Lee, 1992a) presents analysis showing statistically significant evidence of publication bias, but EPA do not consider this issue at all.

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9. Inappropriate data selection for analysis

Some of the relative risk estimates for spouse smoking differ between my Table 3 and those selected in EPA's Table 5-5. I selected my estimates by a defined procedure - choose estimates unadjusted for covariates and use spouse smoking or the index closest to it. The EPA's criteria vary - sometimes using covariate adjusted estimates and sometimes not, and there seem to be clear errors in choice of estimate for some studies. Examples of studies where an inappropriate estimate of relative risk have been chosen include:

Garfinkel case-control : EPA should not have used 1.31 based on "husband's smoking habits at home" when the alternative of 1.23 based on "husband's total smoking habits" was clearly more appropriate for comparability with other studies.

Janerich/Varela : EPA should not have used 0.86 for the estimate, based on ETS exposure in adulthood. EPA should have used, as I did, a weighted average (0.75) of the estimates of 0.93 and 0.44 presented for spousal smoking for direct and surrogate interviews.

Lam 1 : EPA use an estimate of 2.51 based on exposure to smoking spouse, co-habitants and co-workers. The estimate of 2.01 specifically for spousal smoking, though based only on adenocarcinomas, seems more appropriate.

Sobue : EPA use an estimate based on exposure from all co-habitants rather than one based on spousal smoking only. On page 5-15 they note that "much of the ETS exposure appears to result from the co-habitants". This conclusion seems to have been reached from the results, i.e. the higher relative risk in the co-habitants analysis.

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This is of course totally unacceptable, for two reasons. Firstly one must define one's criteria in advance; choosing the highest estimate for any study with multiple estimates will cause obvious bias. Secondly the whole objective of the meta-analysis is to come up with an estimate for risk from spousal smoking and it is of obvious importance that data using an index as close as possible to this be used.

10. Failure to point out the possibility of increased bias in the highest exposure group

The report notes that all 17 individual studies with data by exposure level show a relative risk greater than 1 for the highest exposure categories. This sounds impressive but closer examination reveals there are various difficulties of interpretation not touched upon by EPA. Firstly there are considerable problems due to publication/selection bias of results. Studies that do find an overall association between spouse smoking and lung cancer risk tend to present dose-response data, but many studies that do not find an association do not present such data. Furthermore, in some studies (e.g. Fontham - see Lee (1992b)) authors, faced with a choice of indices of exposure, present detailed results for that index showing the strongest dose-response relationship.

Second, bias due to confounding by other risk factors is also likely to be greater when evaluating heavy spousal smoking. There is convincing evidence (see Annex A) that heavy smokers have greater exposure to other risk factors than do light smokers, and it is to

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be expected that non-smokers married to heavy smokers will also have greater exposure to other risk factors than do non-smokers married to light smokers.

Third, bias due to misclassification of smoking status is also likely to be greater when evaluating heavy spousal smoking. There is evidence (Lee, 1987) that smoking habit concordance rises with amount smoked (i.e. the heavier the smoker the more likely it is that his or her spouse smokes) and the level of misclassification bias depends directly on the level of concordance.

11. Inflation of numbers of deaths due to lung cancer by use of inappropriate "Z-factor" estimates

The approach used by EPA involves three stages:

- (i) obtaining estimates of relative risk associated with spouse smoking directly from epidemiological studies,
- (ii) adjusting these estimates down to account for bias due to misclassification of smoking habit status, and combining them by meta-analysis, and
- (iii) adjusting the combined estimate up to account for the fact that non-smokers married to non-smokers are still exposed to ETS (i.e. for background exposure).

This final adjustment uses an estimate ("Z-factor") of the ratio of cotinine levels among non-smokers married to smokers to those among non-smokers married to smokers. The higher the Z-factor the greater spousal exposure is of total ETS exposure and the

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smaller the adjustment. Conversely, the lower the Z-factor, the greater the adjustment. Suppose for example that the meta-analysis estimate of relative risk is 1.2 and that 50% of non-smokers are married to smoking spouses. The relationship between the value of Z and the proportion of deaths from lung cancer to ETS is then as follows:

| Z    | p    |
|------|------|
| 10   | 0.11 |
| 5    | 0.14 |
| 3    | 0.18 |
| 2.5  | 0.21 |
| 2    | 0.27 |
| 1.75 | 0.33 |
| 1.5  | 0.45 |

Previous analyses have assumed a Z-value of 3. EPA's main analysis assumes a Z-value of 1.75 (based on data by Cummings), thus approximately doubling the number of deaths attributable to ETS. Evidence presented in Layard (1992) and also in presentations to the EPA by R J Reynolds demonstrates that 1.75 is a very low estimate.

12. Inappropriate extrapolation to ex-smokers

Even if ETS does increase risk of lung cancer in non-smokers, there is absolutely no reason why it should increase risk of lung cancer in ex-smokers by the same factor. In discussion on draft 2 various reviewers and members of the Scientific Advisory Board suggested strongly that EPA should make no attempt to extrapolate from non-smokers to ex-smokers in the way that they have done. EPA have ignored this advice for no good reason.

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13. Exposure therefore risk?

In Chapter 4 of the report EPA take the line that ETS can be considered a Group A (human) carcinogen simply because:

- (i) active smoking causes lung cancer,
- (ii) there are "extensive chemical and toxicological similarities between sidestream and mainstream smoke" and ETS is a combination of sidestream and exhaled mainstream, and implicitly because
- (iii) it is assumed there is no threshold dose.

In discussion on the second draft the Chairman of the Scientific Advisory Board, Dr Lippmann, and others made it clear that the above line of argument is not of itself proof that ETS is a human carcinogen, and that the epidemiological evidence needed to be taken into account to come to an overall judgement. EPA have ignored this. Had it been a valid argument, why had it not been applied in, say, 1970? The evidence on active smoking was well established then, the "no threshold", "one molecule causes cancer" theory was popular then in regulatory circles (c.f. the Delaney Clause), and it was obvious that non-smokers had some exposure. The truth of course was that it was assumed, and rightly, that exposure was very much less for non-smokers than for smokers (retained dose of particulate matter differs by a factor of about 2000:1 or more between smokers and non-smokers), and that any risk, even if it existed (many do not accept the "no threshold" argument which at best only operates for cancers caused by some mechanisms), was likely to be very small

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indeed. It was only when Hirayama and Trichopoulos came along in 1981 and suggested quite large risks from ETS that the world started to get interested. The massive 1979 US Surgeon-General report did not even mention ETS as a possible carcinogen in its chapter on involuntary smoking (as it termed ETS exposure).

Of course it remains possible ETS does cause some lung cancers - one can never prove a negative - but the number may be very much less than indicated by EPA.

14. General summary

When one takes into account the lack of association of workplace and childhood ETS exposure with lung cancer risk and the fact that the association of spousal smoking with lung cancer risk seems explicable in terms of bias due to misclassification of smoking habits and confounding, it is difficult to see that a convincing case has been made that ETS causes lung cancer. Additional evidence fortifies this view:- the lack of consistency regarding histological type of lung cancer claimed to be affected, the apparent existence of some publication bias, and the fact that the association with spousal smoking is stronger in studies showing clear lack of comparability between cases and controls in the circumstances in which data were collected.

EPA conceal the relevant data on workplace and childhood ETS exposure, under-estimate the bias due to misclassification of smoking habits, and totally misrepresent the data relevant to the

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possibility of confounding by other risk factors. The additional evidence noted in the last sentence of the previous paragraph is not presented at all, adding to the difficulties of the reader in obtaining a fair view of the evidence. Having obtained a spuriously high estimate of relative risk of lung cancer in non-smokers in relation to spouse smoking (which has not actually been demonstrated to exceed unity), EPA then over-estimate the number of deaths due to lung cancer by over-correcting for ETS exposure in non-smokers married to non-smokers, and adding in, without any real justification, deaths in ex-smokers. The whole process is totally unscientific.

References

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TABLE 1

Risk of lung cancer in relation to workplace exposure<sup>1</sup>

| Study   | Sex | Continent <sup>2</sup> | Relative risk<br>(95% limits) <sup>3</sup> |
|---|-----|------------------------|--|
| Butler  | M+F | U                      | 0.80 (0.25-2.58)                           |
| Foncham   | F   | U                      | 1.34 (1.03-1.73) <sup>4</sup>              |
| Garfinkel (case-control)                        | F   | U                      | 0.93 (0.73-1.18) <sup>4</sup>              |
| Janerich/Varela                                 | M+F | U                      | 0.91 (0.80-1.04)                           |
| Kabat and Wynder                                | F   | U                      | 0.68 (0.32-1.47)                           |
|   | M   |                        | 3.27 (1.01-10.6)                           |
| Kabat   | F   | U                      | 1.00 (0.49-2.06)                           |
|   | M   |                        | 0.98 (0.46-2.10)                           |
| Kalandidi                                       | F   | E                      | 1.70 (0.69-4.18)                           |
| Lee   | F   | E                      | 0.63 (0.17-2.33)                           |
|   | M   |                        | 1.61 (0.39-6.60)                           |
| Shimizu   | F   | A                      | 1.20 (0.70-2.04)                           |
| Wu  | F   | U                      | 1.30 (0.50-3.30)                           |
| Wu-Williams                                     | F   | A                      | 1.22 (0.95-1.57)                           |
| Brownson 1992                                   | F   | U                      | No sig. association <sup>5</sup>           |
| Stockwell                                       | F   | U                      | No sig. association <sup>5</sup>           |
| Combined (fixed-effects meta-analysis estimate) |     |                        | 1.02 (0.93-1.12)                           |
| Combined - US only                              |     |                        | 0.98 (0.88-1.08)                           |

- <sup>1</sup> Data for lifelong never smokers from Lee (1992) Table 3.21 with addition of recently published material
- <sup>2</sup> U - USA, E - Europe, A - Asia
- <sup>3</sup> Relative risks are unadjusted for misclassification of active smoking status, but are adjusted for covariates varying from study to study
- <sup>4</sup> Data for smoke exposure at work in last 25 years, not last 5 years used
- <sup>5</sup> No relative risks or limits were reported; not used in meta-analysis.

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TABLE 2

Risk of lung cancer in relation to childhood exposure<sup>1</sup>

| Study   | Sex | Continent <sup>2</sup> | Relative risk<br>(95% limits) <sup>3</sup> |
|---|-----|------------------------|--|
| Brownson 1992                                   | F   | U                      | 0.80 (0.60-1.10)                           |
| Fontham   | F   | U                      | 0.84 (0.57-1.24)                           |
| Gao   | F   | A                      | 1.10 (0.70-1.70)                           |
| Garfinkel (case-control)                        | F   | U                      | 0.91 (0.74-1.12)                           |
| Janerich/Varela                                 | M+F | U                      | 1.30 (0.85-2.00)                           |
| Kabat   | F   | U                      | 1.68 (0.86-3.27)                           |
|   | M   | U                      | 0.73 (0.34-1.59)                           |
| Koo   | F   | A                      | 0.55 (0.16-1.77)                           |
| Pershagen                                       | F   | E                      | 1.00 (0.40-2.30)                           |
| Sobue   | F   | A                      | 1.42 (0.80-2.51)                           |
| Stockwell                                       | F   | U                      | 1.70 (1.00-2.90)                           |
| Svensson  | F   | E                      | 3.30 (0.50-18.80)                          |
| Wu  | F   | U                      | 0.60 (0.20-1.70)                           |
| Wu-Williams                                     | F   | A                      | 0.85 (0.65-1.12)                           |
| Akiba   | M+F | A                      | No sig. association <sup>4</sup>           |
| Correa  | M+F | U                      | No sig. association <sup>4</sup>           |
| Combined (fixed-effects meta-analysis estimate) |     |                        | 0.96 (0.86-1.08)                           |
| Combined - US only                              |     |                        | 0.96 (0.84-1.10)                           |

<sup>1</sup> Data for lifelong never smokers from Lee (1992) Table 3.23 with addition of recently published material

<sup>2</sup> U - USA, E - Europe, A - Asia

<sup>3</sup> Relative risks are unadjusted for misclassification of active smoking status, but are adjusted for covariates varying from study to study

<sup>4</sup> No relative risks or limits were reported; not used in meta-analysis.

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TABLE 3

Risk of lung cancer in relation to husband's smoking (or nearest equivalent)<sup>1</sup>

| Study   | Continent <sup>2</sup> | Relative risk (95% limits) |                       |
|---|------------------------|----------------------------|-----------------------|
|   |                        | Unadjusted <sup>3</sup>    | Adjusted <sup>3</sup> |
| Akiba   | A                      | 1.52 (0.87-2.63)           |                       |
| Brownson  | U                      | 1.82 (0.45-7.36)           | 1.74 (0.41-7.34)      |
| Brownson 1992                                   | U                      | 0.97 (0.78-1.21)           | 0.81 (0.63-1.03)      |
| Buffler   | U                      | 0.80 (0.34-1.90)           | 0.66 (0.26-1.68)      |
| Chan  | A                      | 0.75 (0.43-1.30)           |                       |
| Correa  | U                      | 2.07 (0.81-5.25)           | 1.53 (0.51-4.55)      |
| Fontham   | U                      | 1.32 (1.03-1.68)           | 1.13 (0.87-1.46)      |
| Gao   | A                      | 1.19 (0.82-1.73)           |                       |
| Garfinkel (cohort)                              | U                      | 1.17 (0.85-1.61)           | 0.98 (0.69-1.40)      |
| Garfinkel (case-control)                        | U                      | 1.23 (0.81-1.87)           | 1.05 (0.68-1.64)      |
| Geng  | A                      | 2.16 (1.08-4.29)           |                       |
| Hirayama  | A                      | 1.39 (0.97-1.98)           |                       |
| Hole  | E                      | 1.89 (0.22-16.23)          |                       |
| Humble  | U                      | 2.34 (0.81-6.75)           | 1.85 (0.57-5.97)      |
| Inoue   | A                      | 2.55 (0.74-8.78)           |                       |
| Janerich/Varela                                 | U                      | 0.75 (0.47-1.20)           | 0.63 (0.38-1.03)      |
| Kabat and Wynder                                | U                      | 0.79 (0.25-2.45)           | 0.66 (0.20-2.20)      |
| Kabat   | U                      | 0.90 (0.46-1.76)           | 0.77 (0.38-1.57)      |
| Kalandidi                                       | E                      | 1.55 (0.87-2.79)           |                       |
| Koo   | A                      | 1.55 (0.90-2.67)           |                       |
| Lam 1   | A                      | 2.01 (1.09-3.72)           |                       |
| Lam 2   | A                      | 1.65 (1.16-2.35)           |                       |
| Lee   | E                      | 1.03 (0.41-2.55)           |                       |
| Liu   | A                      | 0.74 (0.32-1.69)           |                       |
| Pershagen                                       | E                      | 1.03 (0.61-1.74)           |                       |
| Shimizu   | A                      | 1.08 (0.64-1.82)           |                       |
| Sobue   | A                      | 1.06 (0.74-1.52)           |                       |
| Stockwell <sup>4</sup>                          | U                      | 1.60 (0.80-3.00)           |                       |
| Svensson  | E                      | 1.26 (0.57-2.81)           |                       |
| Trichopoulos                                    | E                      | 2.08 (1.20-3.59)           |                       |
| Wu  | U                      | 1.20 (0.48-3.01)           | 1.13(0.43-2.92)       |
| Wu-Williams                                     | A                      | 0.79 (0.62-1.02)           |                       |
| Combined (fixed effects meta-analysis estimate) |                        | 1.17 (1.07-1.27)           |                       |
| Combined - US only                              |                        | 1.13 (1.00-1.27)           |                       |
| - US excluding Stockwell                        |                        | 1.18 (1.02-1.37)           | 0.94 (0.82-1.07)      |

<sup>1</sup> Data for lifelong never-smoking females from Lee (1992) Table 3.14F with addition of recently published material

<sup>2</sup> U - USA, E - Europe, A - Asia

<sup>3</sup> Unadjusted or adjusted for misclassification of smoking status, assuming 2.5% of ever smokers deny smoking, and a concordance ratio of 3.0

<sup>4</sup> Misclassification adjusted estimates cannot be computed as no data are presented giving the breakdown of subjects jointly by case-control and spousal smoking status.

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