

## Letters to the Editor

# Correspondence re: E. T. H. Fontham *et al.*, Lung Cancer in Nonsmoking Women: A Multicenter Case-Control Study. *Cancer Epidemiol., Biomarkers & Prev.*, 1: 35-43, 1991

### Letter

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Fontham *et al.* (1) have recognized that the misclassification bias may have resulted in biased overestimates of the relative risk of lung cancer due to passive smoking or exposure to ETS.<sup>1</sup> That indeed such misclassification occurs is highlighted in the findings of Fontham *et al.*, who reported individual urinary cotinine/creatinine values as high as 14,014 ng/mg in one group of presumably never-smoking controls and as high as 5,163 ng/mg in another group of controls. While nonsmokers typically have such urinary values below 10 ng/mg, Fontham *et al.* used a cutoff value of 100 ng/mg to eliminate from the reported never-smokers those who very likely did not belong in that class.

In their study, Fontham *et al.* used two kinds of controls for their female lung cancer cases: women who had colon cancer and women chosen from the general population. In principle, a passive-smoking investigation should be limited to never-smoking women and, if the actual smokers in the study could be eliminated, the resulting estimate of the relative risk due to passive smoking would be the more valid.

For lung cancer cases, next-of-kin information was obtained in 34% of instances, yet for only 10% of colon cancer controls. The possibilities for bias due to this alone could be extravagant. But that use of next-of-kin information leads in turn to yet another source of bias: urinary cotinine/creatinine determinations could not or were not made for women for whom next-of-kin information was obtained. There were 134 such lung cancer cases but only 32 such colon cancer controls.

As it turned out, the urinary cotinine/creatinine values were much more moderate for the lung cancer cases than for colon cancer or for population controls. Only two lung cancer cases were excluded for being above the cutoff value of 100 ng/mg, those two being at 131 and 219 ng/mg. Of the 260 colon cancer controls for whom such biochemical determinations were made, seven were above the critical value, their values ranging from 145 to 5163 ng/mg, while among 684 population control biochemical determinations, 14, ranging from 103 to 14,014 ng/mg, were above the 100 ng/mg critical level.

To see how this would bias the estimated relative risk, consider that we removed all the current or ex-smokers from among the presumably nonsmoking controls, but none of those from among the lung cancer cases. The misclassification bias would then be worse than if we did nothing, and to an extent that is true if we make such exclusions more certainly from among controls than from among lung cancer cases. And to the extent that Fontham *et al.* have recognized, by trying to correct for it, that the misclassification bias exists, they are conceding that the apparent increased risk due to ETS could be artificial.

To go on: the report by Fontham *et al.* gives me fresh cause for concern. To bring out an increased relative risk from ETS, these investigators switched their attention from all lung cancers to only adenocarcinomas of the lung. No separate attention was focused on other lung cancers, particularly not on squamous cell carcinomas.

If these investigators have had their choice of which type of lung cancer to emphasize, their statistical significance levels should be modified to take the multiple-testing aspect into account. Apparent statistical significance at the 0.05 level would no longer be at the 0.05 level. And even so, the individual comparisons made by Fontham *et al.* are not statistically significant; it was only by going to trend tests, admittedly a sensible approach, that statistical significance could be achieved.

For household exposure to ETS the relative risk of 1.38 for adenocarcinoma would be reduced to 1.21 for all lung carcinomas. That of 1.43 for more than 30 years of household exposure relative to adenocarcinoma would be reduced to 1.25 relative to all lung carcinomas. Even the significant trend test with  $P = 0.03$  would become nonsignificant at  $P = 0.14$  if such reemphasis were made.

With the bulk of the lung carcinomas found being adenocarcinoma (281 of 359 by review diagnosis, 244 of 359 by hospital diagnosis), this reduction in the level of significance with the addition of the squamous cell and other lung carcinomas lends itself to an unusual interpretation. It may well be that for these other lung cancers not only are they not associated with ETS, they may even be negatively associated with ETS. And these others, particularly squamous cell carcinomas, are just the ones most strongly associated by others with ETS.

### **References**

1. Fontham, E. T. H., Correa, P., Wu-Williams, A., *et al.* Lung cancer in nonsmoking women: a multicenter case-control study. *Cancer Epidemiol., Biomarkers & Prev.*, 1: 35-43, 1991.

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<sup>1</sup> The abbreviation used is: ETS, environmental tobacco smoke.