We thank Dr. Weiss for his letter (1). We strongly agree with him regarding the need to defend epidemiologic studies with high-quality data. We wish to point out, however, that Dr. Weiss has not correctly interpreted our data. There is no suggestion in our paper (2) that, as Dr. Weiss puts it, “asbestos exposure [is] associated with a reduction in risk of lung cancer” (1, p. 1462). The paper instead reports that “a significant negative interaction was observed between being occupationally exposed and $GSTT1$: exposed subjects for whom $GSTT1$ was present were at higher risk of lung cancer than exposed subjects carrying the $GSTT1$ null genotype” (2, p. 1036). This is equivalent to the many studies showing that certain genetic variants reduce the risk of lung cancer for smokers as compared with persons with other genotypes; it certainly does not mean that people with these variants should be encouraged to smoke. On behalf of the 42 authors who contributed the data permitting our study, I hope this addresses the misunderstanding that Dr. Weiss, and perhaps others who are less familiar with the field of genetic susceptibility to environmental carcinogenesis, apparently came away with from the paper.

As regards exposure information, we of course agree that such information is vital for drawing definitive conclusions. However, we remind Dr. Weiss and other readers that our paper presents results from a pooled analysis, in which many investigators contributed original data from their own studies. While genotyping methodology has become standard and routine, unfortunately exposure assessment may be quite variable across laboratories, which is why we do not draw any definitive conclusions regarding exposure (defined very loosely as occupational exposure and asbestos exposure). As we indicated in the paper (2), only a small fraction (35 percent) of the subjects had information on occupational exposure, thus making interpretation of the results very limited.
The main point in our article is that contrary to earlier expectations, the glutathione S-transferase theta 1 (GSTT1) null allele is not always a risk factor for lung cancer and other cancers, as it was assumed to be in the past, but has turned out to be protective against some environmental carcinogenic exposures. Similar results have in fact been obtained by a number of laboratories in individual studies including intermediate markers of DNA damage (3–9). As we comment in the Discussion (2), this may be due to the fact that some compounds present in occupational settings are known substrates of GSTT1. Dichloromethane and other halogenated compounds may be metabolized by GSTT1 into mutagenic intermediates; thus, GSTT1-positive subjects might be more prone than GSTT1-null subjects to the genotoxic action of halogenated compounds via the GSTT1 pathway (10).

We thank Dr. Weiss for his interest in our paper and wish to assure him that the “descendants” of Feinstein (11) would be hard-pressed to find any comfort in our article if they understood its content.

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REFERENCES


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