Gene-by-Environment Interaction for Passive Smoking and Glutathione S-Transferase M1?

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In this issue of the Journal, a report by Bennett et al. (1) gives evidence for an interaction in never-smoking Missouri women between exposure to environmental tobacco smoke (ETS) and the homozygous null genotype for glutathione S-transferase (GST) M1 (GSTM1) in increasing the risk of lung cancer. Because GST enzymes act on certain carcinogenic constituents of tobacco smoke to make them excretible, the possibility that the null genotype could confer heightened susceptibility to ETS is plausible. Because 30%–50% of the population carry the null GSTM1 genotype, such an interaction could be an important contributor to lung cancer among never smokers. The finding also provides support with a physiologic rationale for the belief that ETS causes lung cancer in never smokers, although this conclusion is now widely accepted by the scientific community (2,3).

Genetic factors can modify responses to environmental agents, and the report by Bennett et al. (1) represents an important step toward elucidating one such factor. The finding also illustrates that a relatively common genotype, by changing the physiologic response to carcinogenic agents, can contribute measurably to the population burden of disease. Nevertheless, it is natural to be wary of a large interaction between genotype and a low level of exposure to an environmental risk factor, particularly when the evidence for GSTM1 effects on lung cancer risk has been inconclusive in active smokers.

The finding reported here is based on an unusual design, in which only case patients are studied (4), an approach with strengths and limitations. The interaction measure is interpretable as the ratio of the relative risks (RRs) associated with ETS among those with the GSTM1 null genotype versus those without the genotype; a ratio exceeding 1 suggests heightened susceptibility among the GSTM1 null. In a case-only study, this ratio can be estimated only if the exposure and the genotype occur independently in the population. The interaction parameter is then identical to the odds ratio (OR) for the GSTM1 null genotype in relation to ETS among case patients (4). Therefore, in a logistic regression with the use of only case patients, where the outcome modeled is whether the subject carries the GSTM1 null genotype, one can interpret the OR for ETS as an estimate of the same interaction parameter that would be estimated in a corresponding case–control study. Control subjects need not be sampled, saving money and obviating concerns about the appropriateness and possible self-selection of any comparison group; in fact, the estimate of the interaction parameter has greater precision than would be achieved in a similar study that did include control subjects (4).

However, the case-only strategy has notable limitations. First, the independence of the genotype and the exposure under study cannot be verified with the data at hand. (A validation study in which a random subset of control subjects was genotyped would have been helpful.) Second, the genotype-specific ETS RRs cannot be separately estimated with only case patients [although one can do this if the control subjects—for whom all but genetic data have been collected—are included in the analysis (5)]. The value 2.6 estimated by Bennett et al. is the ratio of two genotype-specific ETS RRs. When the authors describe this value (an interaction parameter) as estimating the RR for ETS in the GSTM1 null subpopulation, this inference is not justified. Only if ETS has no effect among those who are not GSTM1 null would 2.6 represent the RR. If we, instead, suppose that ETS is somewhat harmful in those individuals with an active GSTM1 allele, then the 2.6 ratio estimate would imply an RR higher than 2.6 in the GSTM1 null subpopulation.

How credible is this number? Assume that ETS either is neutral or increases risk in the subpopulation that is not GSTM1 null. Algebra reveals that, under independence of ETS and GSTM1, the RR for ETS must be at least the weighted average of the interaction parameter and 1.0, with the interaction weighted by the population prevalence of the deleterious genotype. For example, under an assumed GSTM1 null prevalence of 0.45, the RR associated with ETS would have to be at least 1.7 for the interaction to be 2.6. This implied 1.7 is larger than the 1.24 estimated in a recent meta-analysis (6) and is also larger than the 1.1 reported for the full Missouri study (7). If one begins instead with an ETS RR of 1.16, taken from a recent case–control study carried out in Europe (8), the corresponding ETS–GSTM1 interaction would be, at most, 1.36. The confidence interval provided by Bennett et al. for the interaction estimate of 2.6 does include numbers as low as this, which is reassuring.

Given that a value of 2.6 seems large, possible sources of bias should be considered. First, only 25% of the original never-smoking case patients were genotyped (7), and the availability of suitable tissue could have varied across categories defined by...
ETS and genotype. Retrieving denominators from the original report (7), the availability of genotype information evidently differed according to ETS status: The proportion of subjects included were 51 of 261 and 55 of 170 among ETS-exposed and ETS-unexposed case patients, respectively (P<.01). This disparity heightens concern that the case patients who were genotyped could have been nonrepresentative.

A second potential source of bias is the possible mistaken inclusion of current and former smokers among the “never-smoking” case patients. Many studies demonstrate that a small proportion (range,1%–8%) of active smokers, if asked, will deny having ever smoked. While the estimated percentage of smokers who deny the habit is small, one must also consider that, among people developing primary lung cancer, typically 90% or more are self-reported smokers. If a small proportion of these case smokers deny the habit, they can, because of their numbers, constitute a sizable fraction of the reported never-smoking case patients. Since people with a smoking spouse are more likely to have smoked themselves, it is possible that the ETS interaction detected by Bennett et al. is, in part, an interaction with active smoking. Of course, such an interaction would also be of interest in itself.

Clearly, many questions remain, and the reported interaction (1) between GSTM1 and ETS requires confirmation. Existing studies with archived tissue specimens from control subjects and/or case patients offer opportunities to replicate the result.

As our understanding of “environmental genes” unfolds, other genetic factors will likely emerge as protective or exacerbating modifiers of the response to active and passive smoking. Such factors could, perhaps, be discovered by case-only, case-control, or other innovative epidemiologic approaches. It might be interesting, for example, to carry out a genetic comparison of long-term, elderly, heavy smokers who have beaten the odds with people who developed lung cancer early in life.

REFERENCES