Letter to the Editor

In Response: We appreciate the opportunity to respond to the concern raised about the *GSTM1* and *GSTT1* genotyping methods we used for our recent publication on the relationship between genes in the catechol estrogen metabolism pathway and breast cancer risk. Specifically, Dr. Parl questioned our use of an assay that did not allow for delineation between wild-type homozygotes (+/+) and heterozygotes (+/−). Although we cannot completely rule out the possibility of an increased risk of breast cancer in heterozygotes, it seems unlikely given that previous studies have observed an identical risk (for *GSTT1*) or nearly identical risk (for *GSTM1*) between women with the homozygote variant (−/−) and other women (1, 2), a dichotomy (based on the relationship between genotype and phenotype; refs. 3-6) is the one for which a difference in risk would be the most plausible.

It is conceivable, however, that the risk of the −/− genotype more closely approximates the risk of the heterozygote, and that combining the +/− and +/+ genotypes could obscure potential differences between the +/+ and −/− genotypes. In the two reports cited by Parl as examples of the advantage of more refined genotyping, one study observed that colorectal adenoma risk associated with the +/− genotype was identical to that of the −/− genotype (7), whereas the other study observed that breast cancer risk associated with the −/− genotype more closely resembled that of the +/+ genotype, (2) neither of which provided support for the hypothesis of a gene-dosage relationship. Nonetheless, we acknowledge that epidemiologic studies that can distinguish the heterozygotes from the wild-type homozygotes do offer the ability to uncover patterns of association that could differ from those identified to date through the many studies, including ours, which have not had this level of detail.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. De Jong MM, Nolte IM, te Meerman GJ, et al. Genes other than BRCA1 and BRCA2 involved in breast cancer susceptibility. J Med Genet 2002;39:225–42.
2. Yu K, Di G, Fan L, et al. A functional polymorphism in the promoter region of GSTM1 implies a complex role for GSTM1 in breast cancer. FASEB J 2009, doi:10.1096/fj.08-124073.
3. Lampe JW, Chen C, Li S, et al. Modulation of human glutathione *S*-transferases by botanically defined vegetable diets. Cancer Epidemiol Biomarkers Prev 2000;9:787–93.
4. Brockmoller J, Kerb R, Drakoulis N, Nitz M, Roots I. Genotype and phenotype of glutathione *S*-transferase class μ isoenzymes μ and ψ in lung cancer patients and controls. Cancer Res 1993;53:1004–11.
5. Zhong S, Howie AF, Ketterer B, et al. Glutathione-*S*-transferase μ locus—use of genotyping and phenotyping assays to assess association with lung-cancer susceptibility. Carcinogenesis 1991;12:1533–7.
6. Brockmoller J, Gross D, Kerb R, Drakoulis N, Roots I. Correlation between *trans*-stilbene oxide-glutathione conjugation activity and the deletion mutation in the glutathione-*S*-transferase class μ gene detected by polymerase chain-reaction. Biochem Pharmacol 1992;43:647–50.
7. Moore LE, Huang W, Chatterjee N, et al. GSTM1, GSTT1, and GSTP1 polymorphisms and risk of advanced colorectal adenoma. Cancer Epidemiol Biomarkers Prev 2005;14:1823–7.

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