Growing Pains for the Environmental Genetics of Breast Cancer: Observations on a Study of the Glutathione S-Transferases

Karl T. Kelsey, John K. Wiencke*

Researchers now pursue two distinct avenues of investigation in the search to understand breast cancer susceptibility; one is aimed at highly penetrant genes that confer large absolute cancer risks, while the other focuses on common gene polymorphisms associated with modest individual risk. Among the second group are genes that govern a woman’s defense against environmental exposures. In this context, environment is broadly defined and includes exogenous as well as endogenous agents. The first approach has received the greatest attention and has yielded dramatic results (e.g., BRCA1 and BRCA2), while the second avenue is less traveled and has yet to produce markers with definite clinical or public health utility.

Illustrating this situation is a report appearing in this issue of the Journal by Helzlsouer et al. (1), who describe an association between genetic deficiency in isoforms of the detoxification enzyme glutathione S-transferase (GST), principally GST class mu (GSTM1), and breast cancer. In this rather small prospective study, the significant association of the GSTM1 null genotype with breast cancer is driven by women who were postmenopausal at diagnosis. These investigators also observed a nonsignificant elevated risk for breast cancer in GSTT1 (GST class theta) null individuals and women who had the variant genotype for the GSTP1 (GST class pi) enzyme. When the variant genotypes were combined, a statistically significant, almost fourfold increase in risk was observed for individuals with two or three putative high-risk genotypes.

The reported risk estimates are moderate compared with familial cancer genes, but because of the high prevalence of GST deficiency, Helzlsouer et al. point to the substantial attributable risks for breast cancer that could be linked to these loci. They caution, however, that application of these markers in breast cancer prevention is premature and must await replication in other populations. We agree and note that this report seems to add to a growing list of common genetic variations impugned as potential modifiers of environmental breast cancer risk factors—e.g., N-acetyltransferase (2), CYP1A1 (3), CYP17 (4), and catechol-O-methyltransferase (5).

Problematic is the fact that previous case–control data on GSTM1 are conflicting—some null, but others strikingly similar to those of the study by Helzlsouer et al. An earlier, larger prospective analysis from the ongoing Nurses’ Health Study (6) found no significant association between the GSTM1 deletion and the occurrence of incident breast cancer. How are we to reconcile these seemingly conflicting reports, especially the two prospective studies? Of course, chance may explain the difference. This explanation is both unlikely and unsatisfying. The next simple answer is to note that the confidence intervals of the studies overlap and assume that the true magnitude of the association lies in this “gray zone.”

In addition, because the studies have different base populations, geographic or ethnic variables might lead to distinctly different, but internally correct, results. In the Nurses’ Health Study, case patients were selected from across the United States, whereas all of the case patients in the study by Helzlsouer et al. resided in Washington County, MD. Could differences in the environmental component of the putative gene–environment interaction for breast cancer be responsible for the discordant results? Evidence of heterogeneity in environmental exposures linked with geographic variables is suggested by the Nurses’ Health Study itself; significantly higher adjusted breast cancer risks were reported in California than in the northeastern, midwestern, or southern regions of the United States for postmenopausal women but with little evidence of regional differences in premenopausal disease (7). New approaches to this question that use the powerful methods of molecular biology may be expected to be more sensitive than traditional epidemiologic studies. For example, in the United States, studies of p53 mutation in breast cancer reveal significant differences in the spectrum of mutations and suggest regional differences in etiology. The U.S. population is genetically highly heterogeneous, but even in the Japanese, who are less so, distinctive mutational patterns in the p53 gene have been found in breast cancer arising in different regions of Japan (8). These new lines of evidence point to a diversity of mutational exposure in breast cancer cohorts. Given these observations, it may be critical for future studies of environmental susceptibility genes to incorporate more sophisticated methods of subclassifying breast cancer into etiologically more homogeneous groups. In addition to p53 fingerprinting, approaches such as DNA adduct analysis look highly promising (9–12).

*Affiliations of authors: K. T. Kelsey, Department of Cancer Cell Biology, Department of Environmental Health, Harvard School of Public Health, and Channing Laboratory, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; J. K. Wiencke, Laboratory for Molecular Epidemiology, Department of Epidemiology and Biostatistics, School of Medicine, University of California San Francisco.

Correspondence to: Karl T. Kelsey, M.D., Department of Cancer Cell Biology, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115.

© Oxford University Press
Moreover, the present research raises the following question: In the face of inconsistent population studies and elusive environmental risk factors, what is the appropriate threshold of evidence for accepting a putative gene locus as a candidate for continued exploration by the biological community? We propose that no hard and fast criteria exist, but essential should be the general biologic plausibility of the proposed mode of action of the gene product and the relative potential public health importance of the association. Accordingly, the GSTs have been strongly implicated in a number of environmental cancers (13). In addition, it is well-known that different GST isoforms possess overlapping substrate specificity (14), which is consistent with the interaction of the different GSTs in conferring breast cancer risk as observed by Helzlsouer et al. (1). At the same time, the importance of GSTs in catechol estrogen metabolism, as suggested by Helzlsouer et al., has not been studied extensively (15,16). Furthermore, the role of GSTs in detoxifying lipid peroxidation products is not yet well defined. Thus, while we believe the biochemical rationale for GSTs being involved in breast cancer is not compelling, in the absence of a precise understanding of the estrogen metabolites important for breast carcinogenesis, it seems reasonable to pursue a deeper understanding of glutathione conjugation in estrogen and lipid metabolism. The second critical element for evaluating this threshold, potential public health impact, has been discussed; the potential benefits associated with interventions based on common genetic risks are enormous. A full understanding of the mechanisms involved in gene–environment interactions for breast cancer could lead to effective preventive strategies for millions of women currently at risk. In addition, the interactions involving common genetic variations may also help in the management of risk in those who carry high-risk breast cancer alleles. The way forward is far from clear. However, as the report by Helzlsouer et al. (1) illustrates, the complex environmental genetics of breast cancer are beginning to reveal themselves.

References