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

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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 isozymes 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).

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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

High-Grade Prostatic Intraepithelial Neoplasia: Additional Links to a Potentially More Aggressive Prostate Cancer?

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In this issue of the Journal, Dawson et al. (1) characterize the immunohistochemical distribution of Ret, the protein product of the RET proto-oncogene, in benign, preinvasive neoplastic prostatic epithelium (prostatic intraepithelial neoplasia [PIN]) and in prostate cancer with its spectrum of histologic differentiation. The status of this molecule, common to familial endocrine neoplasia (2), has not been described in the prostate. The authors report overexpression of this proto-oncogene in high-grade PIN (HGPIN) and within histologically less differentiated cancers compared with lower grade prostatic carcinomas. The report by Dawson et al. contributes to a growing literature associating HGPIN and prostate cancer. On the basis of these observations, Dawson et al. speculate that HGPIN is a precursor lesion of the higher grade, poorly differentiated prostatic carcinoma rather than of lower grade tumors.

Studies investigating prostate carcinogenesis and the role of alleged precursor(s) are timely and pertinent. Although recent trends indicate that the epidemic increase in prostate cancer incidence experienced over the last decade is starting to decline (3), the disease continues to be an enormous health care concern. Our limited ability to predict the progression potential and therefore to determine the optimal management of patients newly diagnosed with prostate cancer remains a major hurdle in the fight against this common cancer. This is due largely to the fact that prostate cancer covers a wide biologic spectrum, ranging from an extremely prevalent preclinical form of the disease found at postmortem examination, which appears to develop as early as the third decade of life, to the comparatively much lower incidence of clinically detected cancer (4,5). The course of clinically detected cancer is also widely variable and inconsistent. A significant proportion of patients diagnosed with prostate cancer, including some patients with metastatic disease, die of causes other than their tumors, while others will succumb to this cancer often after a prolonged and declining course. The management and follow-up of patients manifesting an isolated histologic finding of HGPIN on biopsy but having no evidence of carcinoma are also problematic. Experience has documented an approximately 50% chance that a repeat biopsy specimen contains carcinoma when the previous biopsy specimen shows HGPIN only (6,7). Also of importance, however, is a recent report (8) indicating a similar predictive value for the diagnosis of carcinoma on follow-up biopsy of patients found to have atypical small acinar proliferations, which represent proliferative architectural alterations that raise the suspicion for but are not diagnostic of adenocarcinoma. In addition, a lesion that predominantly occurs in the transition zone of the gland, atypical adenomatous hyperplasia, has been suggested as a possible precursor of low-grade prostate cancer; but support for this concept remains largely morphologic (9). Finally, data from the autopsy study at Wayne State University School of Medicine (4) show that some younger men with foci of small cancers have no evidence of HGPIN in their glands. These observations lend support to the idea that there are precursor candidates other than HGPIN that deserve further study.

With these caveats, there are nevertheless compelling reasons to support the role of HGPIN as an important biologic landmark in the complex puzzle of prostate cancer. Studies documenting epidemiologic, morphologic, and molecular/genetic commonalities between the two entities (10–18) continue to mount. Some of these investigations report findings suggesting that HGPIN represents a relatively late event in neoplastic progression (19).

As Dawson et al. (1) suggested, there are indications that HGPIN may not be the universal precursor of all prostate cancers, but it could be associated with particular subsets of cancer. If so, are there clues that these are biologically and clinically more significant and likely to progress? The study referred to earlier from Wayne State University School of Medicine suggests that more extensive HGPIN appears at a younger age in African-American men (20), a segment of the population with a 50% higher incidence of and twice the mortality from prostate cancer compared with Caucasians. Younger African-American men with prostate cancer appear to experience a more aggressive course of disease than older African-Americans or Caucasians of all ages (21). Could these observations suggest a closer link between HGPIN and more rapidly progressive cancers? Some investigators (19) have suggested that the cumulative genetic alterations differentiating HGPIN from normal prostatic epithelium are often greater than those separating the lesion from adjacent prostate cancer. These include parameters of cellular proliferation, DNA ploidy, and the underexpression or overexpression of a number of tumor suppressor gene loci, growth factors, and proto-oncogenes.

The Ret protein investigated in the study by Dawson et al. (1) belongs to the protein tyrosine kinase (PTK) family, which is in turn a member of a large series of proteins known to play important functions in signal transduction. The role of PTK in neoplastic transformation, including possible interactions with chemopreventive agents, has been the subject of intense investigation (22,23). Erb2/neu is the member that has been studied most extensively in prostatic neoplasia. In particular, c-ERBB2 (HER-2/NEU or ERBB2), referred to as the ERBB2 gene, has

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been shown to be overexpressed in both prostate cancer and HGPIN (24). Recent data from a comprehensive review (25) suggest that transcriptional up-regulation rather than gene amplification is the mechanism of RET gene overexpression. In addition to RET, the same review indicates an important role for EGFR/ERBB2 tyrosine kinases in signal transduction. Within the large family of PTK, data on RET proto-oncogene in prostate neoplasia had not been reported previously. Dawson et al. demonstrate a differential in the distribution and intensity of the immunoreactivity with RET in formalin-fixed, whole-mounted sections from radical prostatectomy specimens. With the majority of the tissue sections studied containing areas of benign prostatic epithelium, HGPIN, and carcinoma, Dawson et al. report an increasing positivity among these components in the same order. In addition, higher RET expression correlated with poorer histologic differentiation, and the reactivity of HGPIN was similar to that found in higher rather than lower grade cancers.

Following a long history of inconsistent terminology used to describe atypical lesions of the prostate, some with potential similarity to HGPIN, the latter has been clearly defined more than a decade ago by McNeal and Bostwick (26). During these years, Bostwick and others have investigated this lesion extensively and have added a massive amount of scientific data to the little we had when the term and description of HGPIN were introduced. The number and type of ‘associations’ between this lesion and carcinoma have been striking but do not as of yet constitute evidence for a definitive precursor relationship. While it is still difficult to accurately place HGPIN within the heterogeneous histologic and biologic spectrum of prostatic neoplasia, we have gained substantial knowledge with practical applications. Among those is the high predictability of HGPIN for the presence of prostate cancer discussed earlier. We have also learned, mainly from patients who were treated with neoadjuvant hormone therapy prior to radical prostatectomy, that HGPIN is remarkably susceptible to androgen deprivation therapy (27). Finally, in the last several years, there has been a growing interest in investigating the suitability of patients diagnosed with HGPIN and no proven carcinoma for chemoprevention trials (28,29). As we learn more about HGPIN as a marker for individuals at higher risk for developing prostate cancer, the lesion may prove to be an appropriate target for such promising efforts.

References


