Familial Aggregation: Sorting Susceptibility From Shared Environment

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The contribution of family-based studies to elucidating the etiology of cancer has not been as widely appreciated as deserved. During the past decade, headlines have repeatedly trumpeted the discoveries of many cancer genes. In a number of cases, the discoveries have been translated to the clinic to improve cancer risk assessment and more precisely to devise potential interventions (1–5). In the laboratory, moreover, new avenues have been opened to characterizing the functional role of these genes (6). However, none of this would have been possible without the painstaking research over many years by hundreds of epidemiologists, clinicians, and genetic epidemiologists. They have labored to piece together the puzzle, study by study, on dozens of different cancers involving thousands of patients and their families. When viewed as a whole, this foundation of evidence provides the interpretive framework for the publicized breakthrough studies that capture media attention.

Looking back, it perhaps is not surprising that genetic studies of cancer patients were not a major research goal prior to 1990. While clinical geneticists had long known of and reported rare cancer family syndromes (7), the more common cancers appeared to be largely sporadic (nonfamilial). Epidemiologists searching for susceptibility factors would often choose the achievable and intuitive approach to test for familial aggregation by comparing family histories of case subjects with those of control subjects. Familial aggregation of cancer occurs when cancers cluster in families and one can statistically demonstrate that the risk of the disease in families is greater than the risk in the general population (8). The literature reports scores of studies observing familial aggregation of different cancers by this approach. Such evidence does not automatically mean that these cancers are due to genetic causes. Familial aggregation is an observation that has several interpretations: The cancers can be due to shared environmental exposure(s), shared susceptibility, or a combination of the two. Transmission of environmental factors within families can also mimic or confound true genetic susceptibilities (9). The challenge is to sort through the various hypotheses.

Having demonstrated familial aggregation, how does one next proceed? Today, family-based studies of cancer are very diverse and creative. Armed with new ways to molecularly assay the human genome and new statistical tools, the spectrum of genetic epidemiologic methods now bridges the earlier work of clinicians and epidemiologists. One strategy is to perform a segregation analysis of family histories of probands (affected cases) to test whether patterns of disease transmission through the pedigree are consistent with hypothesized genetic models. Geneticists may want to then move forward with linkage analysis, to localize regions in the genome that carry susceptibility genes (10,11). Once the gene is identified, genetic epidemiologists can characterize patterns of mutations with cancer-related phenotypes (12) and study the interactions of other genes (13), nongenetic factors (14), and interventions (15) that can modify cancer risk. These latter strategies are some of the most exciting challenges for genetic epidemiology: to dissect the relationship of genetic and environmental contributions to cancer.

When genetic epidemiologic studies of diseases are conducted in the context of known nongenetic exposures, the complexity can be daunting, yet potential interactions can be detected. For example, segregation analyses have provided evidence for an age-related susceptibility to lung cancer in the context of smoking exposure (16) and genetic susceptibility to tegumentary leishmaniasis in the context of sandfly exposure (17), while a candidate gene analysis of alcohol dehydrogenase in a case–control study has identified modification of oral cancer risk in the context of alcohol exposure (18).

What about the genetic epidemiology of primary hepatocellular carcinoma (HCC)? When the accumulated research on HCC is examined from this perspective, the inevitable conclusion is that a susceptibility factor (or factors) is (are) likely involved in HCC incidence among persons who are exposed to the hepatitis B virus (HBV) (19). It has long been observed that there is familial clustering of HCC and of HBV (9,19). Thus, studies to elucidate hypothesized susceptibility to HCC necessarily must consider HBV exposure. Of note, Shen et al. (20) performed complex segregation analysis on 490 families ascertained through a proband with HCC and concluded that there was evidence for a major recessive gene that contributed to HCC risk. This analysis included actual test data on HBV infection status of the relatives or inferred this status when such data were missing.

The report by Yu et al. (21) in this issue of the Journal investigated familial aggregation of HCC in the context of HBV exposure by use of two classic epidemiologic approaches. In the first approach, a cohort of 4841 Taiwanese men known to have been exposed to HBV (positive for hepatitis B surface antigen [HBsAg]) were followed for an average of 8.9 years. They were stratified by family history of HCC, and the cumulative risk of incident HCC (n = 129) was compared in family history-positive versus family history-negative subjects. In the second approach (case–control), the 129 cases in the cohort were combined with 429 hospital-based HCC cases in Taiwan (also HBsAg positive). Family histories were compared with those of the non-HCC members of the cohort and were stratified by age at HCC diagnosis in both case subjects and relatives. Neither analysis included data on HBsAg status of the relatives, but the authors presumed that the mothers and siblings were likely to be

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HBsAg carriers. The findings of this study are consistent with the overall body of previous work and provide further insight into dissecting the roles of susceptibility and environment in HCC. A recent study by Tai et al. (22) supplies intriguing evidence for a hypothesized mechanism, longer HBV replication phase, which also clustered in first-degree relatives of HCC patients. It is of great relevance that the familial aggregation analyses of Yu et al. uncovered potential heterogeneity in HCC risk, namely, that younger onset cases tend to occur among HBsAg-positive persons with family histories of HCC. Together, both studies suggest that more research into age-related effects of susceptibility is warranted.

The study by Yu et al. provides further rationale for collaborative investigations between genetic epidemiologists and laboratory scientists to understand the genetics of HCC. As well-characterized cohorts of patients and family members are developed with respect to risk factor exposures (HBV, aflatoxin, diet, alcohol consumption, and tobacco use), along with biospecimen (DNA) collection, more sophisticated studies may be accomplished. It is gratifying that the findings by Yu et al. have added important new pieces to the puzzle of HCC, but we know from our experience with other cancers that much more needs to be done before the specific genes can be implicated and used in public health or clinical applications.

REFERENCES