Genetic Risk and Breast Cancer Survival: Another Link in the Chain of Evidence

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The discovery of the BRCA1 and BRCA2 genes was an important milestone in breast cancer research. Ongoing investigation of cancer genes is sure to improve our knowledge of cancer biology and may speed development of new cancer treatments and prevention strategies. As this research effort goes forward, however, puzzling questions need to be addressed concerning the clinical effects of mutations in the BRCA1 and BRCA2 genes. We do not understand why the degree of cancer risk conferred by mutations is variable or why some mutation carriers develop breast cancer, others develop ovarian cancer, and some develop both. We do not know whether the cancers occurring in mutation carriers are essentially the same or significantly different from those occurring in noncarriers.

Breast cancer occurs at an earlier age in mutation carriers, and a higher prevalence of adverse pathobiologic features has been reported in breast cancers occurring in BRCA1 mutation carriers. (1). These observations raise concern that mutation-associated cancers are more aggressive and result in higher mortality rates. A new study (2) reported in this issue of the Journal addresses the question of cancer survival. Lee et al. found no difference in breast or ovarian cancer survival by mutation status. This conclusion was based on a survey of Ashkenazi Jewish

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volunteers, in which respondents provided information about cancer in family members and were themselves tested for the three breast cancer-related mutations commonly found in this population (the mutations 185delAG [a deletion of two nucleotides] and 5382insC [a single nucleotide insertion] in the BRCA1 gene and the mutation 6174delT [a single nucleotide deletion] in the BRCA2 gene). After a breast cancer diagnosis, relatives of mutation carriers had a 16-year median survival (95% confidence interval = 11–40 years) compared with an 18-year median survival (95% confidence interval = 15–22 years) for relatives of noncarriers. Survival data for ovarian cancer also showed no difference, although study numbers were smaller.

The authors’ use of a community-based sampling technique reduces some though not all of the potential biases encountered when hospital or clinic-based carriers are compared with population-based controls. Screening bias—potentially resulting from greater vigilance and earlier detection in identified carrier families—could provide an appearance of improved survival among carriers (3). Stage of diagnosis is another important variable that must be taken into account when comparing cancer survival among groups. Both worse (4) and improved (5) cancer prognoses have been demonstrated in mutation carriers in studies that did not fully adjust for stage at diagnosis. Because the current study relied on survey data, it lacks a stage-adjusted analysis as well. However, other studies of similar size have included staging data and found no survival differences after adjustment (3,6).

The survey design of the current study also did not allow ascertainment of the true cause of death. Since noncarrier breast cancer cases occurred a decade later than those in carriers, competing mortality from other causes like heart disease could have masked a breast cancer survival advantage in noncarriers. In addition, carrier status was putative, based on relationship to a known carrier; differences between groups could have been diluted by misassignment of carrier status.

Although the study by Lee et al. does not fully resolve the question of survival differences, it adds weight to the evidence indicating a generally similar cancer course in mutation carriers and noncarriers. As in other areas of rapidly evolving genetic knowledge, the final answer must await larger studies, with unbiased selection of cases and controls and objective measures of all relevant outcomes.

When all of the evidence is in, the answer is not likely to be simple. This point is illustrated by accumulating evidence on the breast cancer risk associated with BRCA1 and BRCA2 mutations. Studies of the cancer-prone families who participated in the initial gene discovery studies suggest that the risk of breast cancer by age 70 years in mutation carriers is 84% (7). Yet the survey of Jewish volunteers used by Lee et al. yielded an estimated lifetime risk of only 56% (8). Still lower estimates have been generated by a study of mutation carriers found among sequential Ashkenazi Jewish breast cancer patients unsolicited for family history (average lifetime risk, 36%) (9) and by a population-based study of Icelandic carriers of the 999del5, a 5-base-pair deletion in exon 9 of the BRCA2 gene (37% risk by age 70 years) (10).

There are several potential explanations for these discrepancies. The lower risk estimates are based on analysis of family history data and thus could derive in part from errors in reporting family history. Accuracy of self-reported family history of breast cancer is relatively high, however (11). Differences in risk estimates could also have occurred because the studies reporting lower risks were limited to carriers of a small number of relatively common mutations. Some of these, in particular the 6174delT mutation in BRCA2 (12), may be associated with a lower risk than other BRCA1 and BRCA2 mutations. However, all of the common mutations, including 6174delT, were initially identified in the breast cancer-prone families participating in gene discovery studies; these were defined as families containing four or more cases of female breast cancer diagnosed under age 60 years or male breast cancer at any age (7).

Thus, there are differences in cancer phenotype and degree of family clustering of cancer among carriers with the same BRCA1 and BRCA2 mutations (7–10). This observation indicates the presence of modifying factors that influence the clinical effect of the mutations. Heterogeneity in risk cannot therefore be explained solely by differences in the effect of specific mutations. In this context, it makes sense that the most unbiased sampling methods have yielded the lowest breast cancer risk estimates for BRCA1 and BRCA2 mutations (9,10). These risk estimates are averages, incorporating some mutation carriers with very high risk and others whose risk appears to be only modestly elevated. Aspects of clinical expression other than risk, including cancer survival, are also likely to be variable in mutation carriers.

A full understanding of the clinical implications of mutations in the BRCA1 and BRCA2 genes will require studies that evaluate both the mutations and the factors that modify their expression. These data are likely to emerge slowly, as research is extended from initial small studies using high-risk families to larger studies of subjects representative of mutation carriers within the population. This perspective explains why questions about BRCA1 and BRCA2 mutations that are of great importance to patients and clinicians, including degree and nature of cancer risk and prognosis after cancer occurs, cannot be answered with certainty on the basis of the current evidence. Women considering genetic testing need to be counseled forthrightly about these uncertainties. Even more important, the research agenda must include methods for the identification and study of the factors that modify the effect of genetic risk. These are likely to provide vital clues to carcinogenesis and cancer treatment and are as important to the study of cancer genetics as the genes themselves.

REFERENCES