BRCA1 and BRCA2: a Small Part of the Puzzle

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The article by Peto et al. (1) in this issue of the Journal reports a low prevalence of BRCA1 and BRCA2 gene mutations among women with early-onset breast cancer. It also provides new information about the complexity of breast cancer genetics: The study results indicate that increased cancer risk among relatives of affected women is only rarely attributable to BRCA1 and BRCA2 mutations and often subject to the modifying effect of other factors.

Among women with breast cancer diagnosed before age 36 years, the study found that only 5.9% carried an identifiable BRCA1 or BRCA2 mutation. The percentage was even lower, 4.1%, for women with breast cancer diagnosed between the ages of 36 and 45 years. Because some mutations may be missed by current molecular techniques, Peto et al. estimate that the true percentages of mutation carriers are 9.4% and 6.6%, respectively, for the two age groups; even with this correction, BRCA1 and BRCA2 mutations account for only a small part of the disease burden of breast cancer. These data are consistent with previous population-based studies of the prevalence of BRCA1 mutations among young women with breast cancer in North Carolina (2), western Washington (3), and Australia (4).

The investigators collected family history data for study subjects and used a cancer registry to confirm positive family histories. They then compared the number of cases of breast cancer in relatives to the number expected from population data. As expected, significantly more cancers occurred in relatives of BRCA1 and BRCA2 mutation carriers than would be expected from population rates. Cancer incidence was also substantially elevated in relatives of nonmutation carriers. The latter observation tells us that genetic risk is an important contributor to breast cancer well beyond the small number of families who carry BRCA1 and BRCA2 mutations. However, the breast cancer incidence in noncarrier families was lower than the incidence in families carrying mutations in BRCA1 or BRCA2 families.

Thus, the additional genetic factors in these families, which are yet to be discovered, are likely to be more subject to modifying environmental and genetic factors than BRCA1 and BRCA2 mutations.

The number of breast cancers among relatives of BRCA1 and BRCA2 mutation carriers was also compared with the number predicted from observations in the highly penetrant cancer-prone families who participated in the initial gene discovery studies. For these high-risk families, the risk of breast cancer in female mutation carriers reaches 84%–87% by age 70 years (5,6). For relatives of BRCA1 and BRCA2 mutation carriers in the current study, breast cancer incidence was only a little more than a third of the incidence seen in the initial cancer-prone families. Thus, the incidence observed by Peto et al. is, in fact, much closer to estimates derived from other less selected populations that suggest a lifetime risk of breast cancer in the range of 36%–56% for carriers of BRCA1 and BRCA2 mutations (7–9).

This observation adds to the evidence that BRCA1 and BRCA2 mutations are also subject to powerful modifying effects. In families where these mutations are highly penetrant, adverse modifiers may be present, enhancing the effect of the mutations on cancer risk. Conversely, among mutation carriers whose family history is more benign, modifiers that limit the carcinogenic effect of the mutations may be present.

As the authors acknowledge, the study was limited by retro-
spective determination of mutation status. As a result, women who died within a short time after diagnosis were underrepresented among study subjects. Whether BRCA1 or BRCA2 mutations affect breast cancer prognosis is an unresolved question. Studies have found worse breast cancer survival in mutation carriers compared with persons without mutations. If BRCA1 and BRCA2 mutations are, in fact, associated with a worse cancer prognosis in young women, the current study may have underestimated the contribution of these mutations to early-onset breast cancer. Assessment of risk in family members was also limited by the collection of data on relatives other than first-degree relatives in only a portion of the study subjects. In addition, the authors may have overestimated the heterogeneity of their “outbred” study population, which consisted wholly of white women residing in Britain; this population is likely to be considerably more homogeneous than a representative U.S. population would be. Despite these limitations, the study provides convincing evidence that the proportion of breast cancer cases attributable to BRCA1 and BRCA2 mutations is low and that inherited risk for breast cancer is subject to the effect of modifiers.

An important aspect of this study is that it documents a pattern likely to be repeated in other cancers: Genes will be identified initially through linkage studies by use of the highest risk families and, thus, will yield data that tend to overestimate the risk associated with gene mutations. Only as more representative populations are studied will the variability of inherited risk become apparent. A key question is whether the modifying factors that influence inherited risk are themselves modifiable. These factors are likely to be diverse and may include environmental exposures, personal behaviors, and mutations in genes other than BRCA1 and BRCA2. As these modifiers are identified, it is reasonable to assume that some will prove amenable to manipulation and others will not. Investigation of this aspect of inherited cancer risk represents an urgent research priority. The answers emerging from such research are likely to contribute significantly to defining new opportunities for cancer risk reduction.

Although accumulating evidence indicates that mutations in the BRCA1 and BRCA2 genes are only a small part of the puzzle of inherited risk, the lessons to be derived from BRCA1 and BRCA2 research are profound. Genetics has left the era of monogenic disease and entered the era of complex, gene–environment interactions—in short, genetics has entered the world of common diseases. The research challenges involved in exploring this world are daunting, but they represent the next important step in addressing the problem of cancer.

**REFERENCES**