Cancer Risks in BRCA1 Carriers: Time for the Next Generation of Studies

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Estimating the risk of cancer in individuals who carry a germ-line mutation in a cancer susceptibility gene or who are related to known mutation carriers has profound clinical implications. Each day, women and health care providers use information about the risks conferred by BRCA1 to help make intelligent choices regarding screening, chemoprevention, and risk-reducing surgery. Several studies have already demonstrated the measurable benefits of tamoxifen for women at high risk for breast and ovarian cancer (1) and a lowered risk in women who have undergone bilateral mastectomy (2) or salpingo-oophorectomy (3). Therefore, it makes sense to estimate risks as carefully and precisely as possible and to expand our knowledge of other cancer risks associated with BRCA1 in the hope that targeted strategies for risk reduction will also be relevant for these cancers.

Two articles in this issue of the Journal describe the lifetime incidence and risk of cancer in BRCA1 carriers (4,5). Both groups of investigators have previously shown that the risk of breast and ovarian cancer is substantially increased in women carrying a deleterious BRCA1 mutation (6,7). The article by Brose et al. (4) in this issue of the Journal is based on families of patients from a cancer risk assessment clinic and confirms that deleterious BRCA1 mutations are associated with high risks of breast and ovarian cancer. Although the study of Brose et al. does not substantially advance our current understanding of lifetime risk estimates for breast or ovarian cancer, it suggests risks of cancers of the uterus, fallopian tube, prostate, colon, pancreas, lung, and stomach, and of melanoma. The study by Thompson et al. (5) is based on the Breast Cancer Linkage Consortium (BCLC) families and examines a variety of cancers other than breast and ovarian. Although it is generally recognized that risk estimates from the family-based study design used by both of these groups are overestimated compared with those from population-based studies (8), data from high-risk families such as these can be helpful in clarifying risks to families that present for genetic counseling when analyzed carefully.

At first glance, these two articles offer similar perspectives on the risk of other cancers among BRCA1 carriers. Both studies identified families ascertained on the basis of multiple affected family members with breast and/or ovarian cancer or women diagnosed with breast cancer at a younger age. Both studies analyzed the incidence of cancers in family members who carry BRCA1 mutations. Indeed, both studies identified statistically significant increased risks of pancreatic cancer and colon cancer among BRCA1 carriers, although other cancer risks are less consistent between the studies. But even the pancreatic and colorectal cancer results do not necessarily represent independent confirmation of the same findings, because 97 of the North American families included in the study reported by Thompson et al. are among the 147 families described in the article by Brose et al. Thus, 14% of the data from the BCLC study overlap with data from the Brose study, and 66% of the data in the Brose study are contained in the BCLC study.

A closer look reveals some important differences between these studies. Although the eligibility criteria for families in these two studies were nearly identical, the analytic methods are quite different and need to be carefully considered when interpreting the findings. Thompson et al. estimated relative risks with the use of standardized incidence ratios (SIRs), a classic technique that compares the number of observed cancers with the number of expected cancers within the cohort at risk, based on incidence rates that account for age, sex, time trends, and geographic differences. Brose et al. used a simpler method to estimate relative risk that compares the cumulative age-adjusted risks among BRCA1 mutation carriers with the cumulative age-adjusted population risk reported from the Surveillance, Epidemiology, and End Results [SEER] Program. Although this may seem to be a reasonable approximation of relative risk, this approach does not take full advantage of the data and makes it much more difficult to interpret the statistical significance of their findings.

The two groups also took different approaches to estimating the probability that family members have a BRCA1 mutation. Many individuals were tested directly, making it easy to confirm the presence of a mutation. However, for family members that had not been tested, Thompson et al. used a quantitative approach to estimate a weighted probability of being a mutation carrier, whereas Brose et al. defined presumed carriers by use of a form of pedigree analysis that used data only from a subset of family members.

So how can we interpret these data? First, Brose et al. confirm that BRCA1 mutations confer a very high lifetime risk of developing cancers of the breast, ovary, and fallopian tube. However, BRCA1 appears to increase only slightly the risk of other cancers, and more work is needed to clarify the differences in risks reported in the two studies. The data of Brose et al. suggest that stomach cancer is worth investigating further, but Thompson et al. do not make a compelling case for an increased risk of stomach cancer associated with BRCA1. In both studies, BRCA1 does appear to be associated with a more than doubled...
risk of pancreatic cancer. The association is stronger among younger patients and is observed in both men and women, although overall the risk is lower than that observed for BRCA2 and may merit further research. However, the clinical implications of this association with pancreatic cancer are not yet apparent, because enhanced surveillance for pancreatic cancer currently seems unlikely to offer advantages to patients and could trigger harmful invasive investigations or treatment.

The relationship between BRCA1 and colorectal cancer remains puzzling. Both of these studies suggest that BRCA1 mutations may confer a small, but measurable, increased risk of colon cancer. But why is this risk observed only among women, and why is there such a remarkable difference between the risk of colon cancer and the risk of rectal cancer? The data from the BCLC study show that BRCA1 carriers were twice as likely to report colon cancer (SIR = 2.0, 95% CI = 1.45 to 2.85) but were statistically significantly less likely to report rectal cancer (SIR = 0.23, 95% CI = 0.09 to 0.59). The combined data from these sites show no statistically significant increase in the risk of colorectal cancer (SIR = 1.25, 95% CI = 0.91 to 1.72) overall. However, among women, an increased risk of colon cancer is observed, as well as an increased risk for cancer of the colon and rectum combined. As suggested by Thompson et al., this observation may very well indicate that some ovarian cancers were incorrectly reported as colon cancers among women and that rectal cancers may have been misclassified as colon cancers among both men and women. Misclassification of the primary tumor site may also explain the statistically significantly increased risk of cervical and other uterine cancers noted by the BCLC.

The literature is fairly consistent in recognizing a rather strong association between prostate cancer and BRCA2. But the BCLC study sheds new light on the relationship between BRCA1 and prostate cancer, suggesting that there is a modest, nearly twofold higher risk for carriers than for non-carriers. The effect is observed only among those with a younger age of onset, and the relative risk is more apparent among European centers than among North American centers, where screening practices might make it more difficult to appreciate an association. For low-penetrance susceptibility genes, one might typically consider clinical recommendations that reflect advice as simple as “follow current screening guidelines.” However, if subsequent studies confirm the association between BRCA1 and early onset prostate cancer and if prostate cancer screening is shown to be of benefit in ongoing randomized trials, the timing of screening guidelines may need to be adjusted.

Where do we go from here? Both of these studies provide intriguing new patterns to investigate further, and it is now time for the next generation of studies to follow each lead more directly. Family studies that rely on self-selected or referred families are vulnerable to ascertainment bias that is difficult to correct, even when analyzed as carefully as the study by Thompson et al. We need to directly measure the risks associated with BRCA1 in population-based studies of each disease of interest. Cohort studies of BRCA1 carriers who are representative of the general population are ideal. However, these studies are complicated, expensive, and time-consuming when planned prospectively. Retrospective cohort studies are perhaps even more logically complicated but feasible, although issues of consent for genetic testing would have to be addressed carefully. Population-based case-control studies of prostate, colorectal, pancreatic, and stomach cancer are unlikely to be vulnerable to the same types of ascertainment bias that complicate family studies, and these studies will provide data regarding the relevance of BRCA1 mutations to the development of each disease. In the meantime, the message is that the major cancer risks conferred by BRCA1 are related to cancers of the breast, ovary, and fallopian tube, but increased risks of other cancers are likely to be small.

REFERENCES


NOTE

Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.