Study Clarifies Risk of Breast, Ovarian Cancer Among Mutation Carriers

Women who inherit mutations in the BRCA1 and BRCA2 genes may have high lifetime risks for breast and ovarian cancer regardless of whether they have a family history of the cancers. That finding comes from the New York Breast Cancer Study (NYBCS), the most thorough analysis to date of cancer risks among women who carry the mutations. Risk levels found in the NYBCS are similar to those reported in most earlier studies, typically done in families with several cancer cases over multiple generations. But other studies have come up with lower risk estimates, and some scientists questioned whether the preponderance of families with strong cancer histories—who provided invaluable clues early in BRCA1 and BRCA2 research—might have led to an overestimation of risk for other carriers. Might there be “low-risk” families that carry a mutation but are protected against cancer by some other genetic or environmental mechanism?

The answer may be no. Instead, the NYBCS researchers found that some BRCA1 and BRCA2 families have few cancer cases simply because they are small, have more men than women, or include mostly women who inherited normal copies of the genes from both parents. They found that by age 80, a woman with a mutation in either gene has an 82% risk of developing breast cancer, compared with an average woman’s risk of about 13%. Risks were 20% by age 40 and 55% by age 60. Lifetime risks for ovarian cancer were 54% for women with BRCA1 mutations and 23% for those with BRCA2 mutations.

Published in the October 24 issue of Science, the NYBCS was led by breast cancer genetics pioneer Mary-Claire King, Ph.D., of the University of Washington, Seattle; Joan Marks, founder and director emerita of the first genetic counseling graduate program at Sarah Lawrence College in Bronxville, N.Y., in 1969; and Jessica Mandell, certified genetic counselor and research coordinator. They enrolled 1,008 New York-area Ashkenazi Jewish women diagnosed with breast cancer at 12 medical centers in New York, New Jersey, and Connecticut from 1996 to 2001.

“We tried to get the truest estimate of risk by looking at women who came from a variety of family histories,” Mandell said. “Some had very strong histories of breast and ovarian cancer, and others had virtually no history.”

The Ashkenazi population, which includes the vast majority of American Jews, is ideal for studying BRCA1 and BRCA2 because nearly one in 40 Ashkenazi Jewish individuals has one of three known ancient mutations in the genes. People of other ethnic backgrounds may have mutations scattered across the genes, so testing can be more difficult and expensive. But the researchers said their findings apply to all BRCA1 and BRCA2 families regardless of ancestry.

In contrast to previous studies that used patient reports of family history and statistical modeling to estimate risk, in the NYBCS both the probands (initially identified breast cancer patients) and their close relatives were directly tested for BRCA1 and BRCA2 mutations. In some cases, deceased relatives had tissue specimens available for testing, whereas other ancestors’ mutation status could be reconstructed from data on living relatives.

Of the 1,008 probands, 104, or 10.3%, had one of the three mutations. A surprise finding was that 52 of these women—precisely half—had no breast or ovarian cancer among mothers, sisters, grandmothers, or aunts. In most cases, family testing revealed that these women had inherited the mutation from their fathers.

To discover whether these families were truly “low-risk,” the researchers scrutinized them in greater detail, assessing breast cancer risk among more distant relatives including third and sometimes fourth cousins. They found that risks among mutation carriers in these families did not differ significantly from risks in other BRCA1 and BRCA2 families. In other words, “low incidence is not synonymous with low risk,” the authors wrote.

Sharon Plon, M.D., Ph.D., a geneticist at Baylor College of Medicine, Houston, co-authored a “Perspectives” article in Science to accompany the NYBCS publication. In an interview, she said the NYBCS produced a “tighter” risk estimate than other studies have been able to, but one that is comparable in magnitude with earlier findings.

Other findings from the study offer both good and bad news for women in BRCA1 and BRCA2 families. On the worrisome side, breast cancer risk appears to be increasing with time. Among mutation carriers born before 1940, 24% of the women had breast cancer by age 50. But among those born after 1940, 67% were diagnosed by that age.

“The increase in breast cancer risk over time parallels, at much higher levels, the increase in breast cancer risk among women generally,” the authors wrote. Although changes in reproductive patterns, such as having children later in life, may explain part of the cohort difference, Mandell said that the
finding also suggests that unknown environmental factors may play a role, and the NYBCS should spur further research into these areas.

Plon suggested that the rising risk in younger women might be explained by the additive effect of known risk factors (such as age at menarche and at first pregnancy) but that the study lacked sufficient statistical power to evaluate these variables in combination. “Or, there may be factors we haven’t considered at all,” she said. “It will take much larger studies to sort this out.”

“The cohort difference is important,” she added, “because the women we are now counseling were primarily born after 1940.”

More encouraging was the suggestion that young women (either with or without BRCA1/2 mutations) can take action to delay, if not prevent, the onset of breast cancer. Women in the study who exercised and maintained a healthy weight during adolescence had a later onset of breast cancer compared with inactive or overweight women. Of many potential risk modifiers the scientists examined, including smoking and alcohol drinking, exposures to radiation and pesticides, and reproductive behaviors, the other only factor to influence risk was that women who had at least one pregnancy also had later cancer onset.

In the past, Mandell said, uncertainties about risk “allowed health care professionals to provide only ranges of risk for their patients, and patients would have to make decisions based on incomplete information. Our study helps to validate that the risks are indeed very high.” The new findings, she said, suggest that some women, such as those of Jewish ancestry who are diagnosed with breast cancer at a relatively early age, should get genetic counseling—and possibly testing—even in the absence of a family history of the disease. In particular, she said, because breast and ovarian cancer are women’s cancers, many cases inherited through the paternal lineage have likely been missed.

Plon agreed. “Even among physicians, I think there is a lot of misunder-

standing about autosomally inherited conditions,” she said. “By and large, they will ask women about breast cancer history on the mother’s side of the family, but will not ask about the father’s side.”

King said the NYBCS findings highlight the potential value of genetic testing both for women who carry mutations and those who do not.

“If one is the relative of an identified carrier, it can be important to be tested rather than assuming one is at high risk, because 50% of the daughters and sisters of mutation carriers will not have inherited the mutation of the family,” she said. “The risks of breast and ovarian cancer among carriers versus non-carriers are very different, and genetic testing can identify the group in which one belongs.”

In their Perspectives article, Plon and co-author Ephrat Levy-Lahad, M.D., of Hebrew University, Jerusalem, wrote that the NYBCS provides “definitive cancer risk figures” for women who carry the gene mutations and have at least one relative with breast cancer. But they question whether the study might still overestimate risks for other carriers because all its probands, at least, had breast cancer.

Plon and Levy-Lahad further asserted, “Results of the NYBCS suggest that the time has come for research studies to examine testing for BRCA1 and 2 mutations in the general population to determine if cancer risks are sufficient to justify general screening.”

King believes that, in the modern American population, the possibility of truly low-risk BRCA1/2 families has been ruled out by the high incidence of breast cancer among mutation carriers who are distant relatives of probands in low-incidence nuclear families. However, she said, “The possibility of truly low-risk families cannot formally be excluded in populations with lifestyles very different from modern America. Women’s experiences in other times and places might not lead to early expression of breast cancer among mutation carriers. There could be contexts in which the age-at-diagnosis curve is sufficiently delayed [so] that a larger fraction of mutation carriers escape breast cancer entirely.” Such an effect would more likely be social than confined to individual families, she said.

Said Plon, “this study argues that we may want to look at, on a research basis, screening women from Ashkenazi Jewish populations for these mutations regardless of family history, because 50% of the mutation carriers [the NYBCS researchers] identified had no family history at all. The only way they were identified was that they were diagnosed with breast cancer themselves. But if we want to do something in a preventive mode, we need to identify these women before they develop cancer—take Ashkenazi Jewish women at age 35, for example, and do a study to test them, identify the mutation carriers, and counsel them about surveillance and prevention measures.”

King added that “because of the extremely broad spectrum of mutations in these genes, such studies can realistically only be carried out in founder populations” with known stable mutations.

For the present, however, Mandell said, “I don’t think any medical professional would say that general population screening is warranted.” Overall, only
5% to 10% of all breast cancer is inherited, and even among Jewish women, only about 2.5% carry BRCA1 or 2 mutations. These small proportions, she said, suggest that screening would be inefficient and not cost-effective.

Also, she said, “testing for these mutations is not just a medical situation … it encompasses a lot of very personal, emotional information about potentially carrying a risk for a medical condition and one that you could pass on to your children. It really becomes a family situation, and with confidentiality and insurance issues, these factors play into a woman’s decision about whether to be tested.”

The delayed-onset effect from exercise and weight control was seen in women with and without BRCA mutations, Mandell noted, so it may be the finding with the widest implications.

“Having a good exercise routine and a good diet seem to go a long way for future breast cancer protection,” she said. “And while that may not help women who have cancer already, it certainly is information that may help their daughters and other relatives.”

Plon and Levy-Lahad also noted that the NYBCS may have lessons to offer researchers performing genetic studies of other diseases.

“I think there has been a feeling that in conditions where there were clear dominant mutations, environmental or lifestyle factors would have relatively small effects on risk,” Plon said. “This study argues that’s not the case—that other factors like the birth cohort can influence risk substantially.”

—Tom Reynolds

Editor’s note: Journal News Correspondent Tom Reynolds, 44, died in a car accident November 6. Tom began writing for the Journal in 1991, when he joined the National Cancer Institute’s Mass Media Branch. In 1995, he worked from London as the Journal’s European correspondent. He left NCI in 1997 to work in the Dean’s Office of Harvard Medical School, and he continued to write on a freelance basis for the Journal and other publications. He wrote more than 150 articles for the News.