Risk Reduction Works for BRCA Mutation Carriers—With Heavy Costs

Ten years of research suggests that surgery effectively prevents breast and ovarian cancer in women with BRCA1 and BRCA2 mutations. The risk reductions are substantial, but the approaches are drastic—prophylactic removal of the breasts or ovaries—leaving many women and their doctors looking for better ways to fend off the diseases.

BRCA1 and BRCA2 mutations were discovered in 1994 and 1995, respectively. “In 10 years, we’ve gone from not knowing whether or not any of our risk reduction strategies work to really having strong evidence that we can alter the natural history of these inherited cancer syndromes and reduce the risk of getting breast or ovarian cancer,” said Noah D. Kauff, M.D., a gynecologist and geneticist at Memorial Sloan-Kettering Cancer Center in New York. “We believe this will translate into a survival advantage, but the data are not yet available.”

However, the problems with prophylactic surgery have researchers hunting for alternatives; studies of intensive screening and lifestyle factors, such as oral contraceptive and alcohol use, may offer some clues. “Over the next 10 years, we want risk reduction strategies to be less drastic and not require removal of the organs at risk,” Kauff said.

Population at Risk

Most breast and ovarian cancers are considered sporadic, with no known genetic link. Only about 10% of women with breast cancer have a genetic predisposition, such as mutations in BRCA1 or BRCA2. BRCA mutation carriers face a lifetime risk for breast cancer estimated between 36% and 85% and a risk for ovarian cancer between 16% and 60%. (By comparison, the lifetime risk in the general population of breast cancer is about 13% and of ovarian cancer is 1.5%).

“Half a million U.S. men and women are BRCA1 mutation carriers, and half of those are women,” said Alice S. Whittemore, Ph.D., professor of epidemiology and biostatistics at the Stanford University School of Medicine in California. In 2004, she and her colleagues produced the first data on the U.S. prevalence of BRCA1 mutation carriers in the U.S. non-Hispanic white population using two population-based series of San Francisco Bay area patients with invasive breast or ovarian cancers. They estimated a carrier prevalence of 0.24% in non-Ashkenazi whites and 1.2% in Ashkenazi Jews, and they are now working on prevalence estimates for minority women.

The most obvious option for breast cancer risk reduction in BRCA mutation carriers is prophylactic mastectomy. Several studies in mutation carriers indicate that it could provide a 90% reduction in breast cancer risk. But researchers agree that, despite the dramatic risk reduction, other options are needed. “I certainly hope that by the mid-21st century, prophylactic mastectomy will be in the category of bloodletting, since it is so drastic and disfiguring,” Whittemore said.

Removal of the ovaries can reduce risk for both breast and ovarian cancers. At this year’s annual meeting of the American Society of Clinical Oncology, Kauff presented 4-year follow-up data for BRCA mutation carriers who underwent removal of the fallopian tubes and ovaries—called risk-reducing salpingo-oophorectomy (RRSO). The surgery was associated with a 70% lower risk of breast cancer and 83% lower risk of ovarian cancer.

“In terms of decision-making, we’re seeing one thing very clearly,” said Marc D. Schwartz, Ph.D., associate professor of oncology and co-director of cancer control at Georgetown University Lombardi Comprehensive Cancer Center in Washington, D.C. “Prophylactic oophorectomy is elected far more than prophylactic mastectomy.” Because oophorectomy reduces the risk for both cancers, he is seeing women who don’t want bilateral mastectomy choosing prophylactic oophorectomy. Plus, he said, “ovarian cancer screening is less effective than breast cancer screening. So for women with a family history of ovarian cancer, oophorectomy may be considered the best option for ovarian cancer risk management.”

At Memorial Sloan-Kettering, 65% of women with BRCA mutations elect to undergo RRSO and only one-third elect prophylactic mastectomy, according to Kauff. “The majority of women who elect mastectomy also have RRSO,” he added. “And those who choose neither participate in intensive breast and/or ovarian cancer screening as appropriate.”

For RRSO, the decisions don’t end with the surgery. The loss of the ovaries can result in menopause-like symptoms, including hot flashes, vaginal dryness, and night sweats. Hormone replacement therapy (HRT) can help treat these symptoms but HRT can increase a woman’s risk of breast cancer.

Although Kauff does not put all his RRSO patients on HRT, “most people in the field think they’re still much better off from a breast cancer standpoint on HRT than if they have ovaries in situ,” he said. But if symptoms can be handled with local hormonal therapies, such as low-dose vaginal estrogens, which have less systemic absorption, Kauff tries those first. Karen H. Lu, M.D.,
co—medical director of clinical cancer genetics at the University of Texas M. D. Anderson Cancer Center in Houston, will watch for symptoms of menopause in her patients and, if the symptoms are bothersome, treat with low-dose estrogen replacement. “The goal is short-term use [of hormones],” she said.

“We’re convinced that RRSO is the best of bad options,” Kauff said. “It clearly has its downsides. However, until better nonsurgical risk reduction strategies are available, it is a procedure that all women at inherited risk should at least consider.”

Other Options

Many mutation carriers are choosing MRI screening in combination with mammography instead of prophylactic surgery, according to Schwartz. “Insurance doesn’t typically cover MRI yet, and we don’t have impact data on mortality yet. But evidence suggests that MRI can pick up lots of breast cancers not picked up by mammography,” he added. Costs for MRI vary but run at least $1,000. Schwartz is conducting a study to examine long-term outcomes in women with BRCA mutations who choose screening over surgery and psychosocial outcomes in women who choose bilateral mastectomy over screening.

In the search for other alternatives to surgery, the NCI-supported Collaborative Family Registry for Breast Cancer Studies, which includes investigators in the United States, Canada, and Australia, is amassing data on 800 women with and without breast cancer who carry deleterious BRCA mutations. The study will examine alcohol and tobacco use, radiation exposures, physical activity, oral contraceptive use, and reproductive factors, all of which contribute to breast cancer risk. However, the women come into the study from high-risk clinics, so it’s not a truly random sample of all BRCA mutation carriers. “Ideally, we would follow carriers who are free of breast cancer and look forward, but many are having prophylactic mastectomy,” Whittemore explained. Results are expected in a year.

One avenue under investigation for ovarian cancer prevention is oral contraceptive use. “We’ve known for years that oral contraceptive users have substantially reduced risk—50% lower—for ovarian cancer,” said Mark H. Greene, M.D., chief of NCI’s Clinical Genetics Branch. “So we’ve wondered about the BRCA mutation carriers. A 2004 American Journal of Epidemiology study by Whittemore found the same lowered risk associated with oral contraceptive use for women with BRCA mutations. "The pendulum is swinging toward supporting the belief that oral contraceptives may reduce risk in BRCA1 and BRCA2 patients,” Greene said. “But it’s a potential double-edged sword, because of the breast cancer risk with estrogen. This is a classic example of the tightrope walk between risk and benefit of actions we take. Breast cancer is much more common than ovarian cancer.”

From the data she’s seen, Whittemore knows what she would do. “I’m not sure everyone would agree, but if someone has had prophylactic mastectomy but wants to keep her ovaries to have children, then oral contraceptive use [in between efforts to conceive] is probably a good option” for ovarian cancer protection, she said. For a woman who still has her breasts, the story may be different. “Putting myself psychologically in the shoes of a young woman with a BRCA1 mutation, I certainly would get MRI screening of the breasts. I would be religious about it,” Whittemore said. “I would not have a mastectomy. I would just get very good screening.”

Because of improvements in surveillance, Kauff seems to agree. “We may be approaching a time where it is a reasonable strategy to consider a combination of RRSO at conclusion of childbearing combined with intensive screening with mammography and MRI as a reasonable alternative to prophylactic mastectomy.”

The Unanswered Questions

Kauff’s group is now trying to determine the best timing for RRSO, looking for differences between BRCA1 and BRCA2 mutation carriers. For BRCA1 mutations, ovarian cancer risk appears during a woman’s late 30s. For a woman with a BRCA2 mutation, risk doesn’t really begin until her late 40s, early 50s. “For BRCA2, screening into the late 40s, early 50s, may not be unreasonable,” he said.

Researchers expect some answers from an NCI-supported study run by the Gynecologic Oncology Group that will compare 1,000 women who choose RRSO with 800 women who go for intensive ovarian cancer screening. Women are being enrolled nationally and will be monitored for 5 years.

The screening protocol, devised by Steven J. Skates, Ph.D., of Massachusetts General Hospital in Boston, involves annual transvaginal ultrasound plus serial CA125 measurements four times a year. All the women will receive a detailed assessment comparing quality of life, sexual functioning, frequency of menopausal symptoms, depression, anxiety, cancer worry, and concerns associated with familial risk of ovarian cancer. Serum will be collected every 3 months to evaluate promising markers and genetic alterations relevant to ovarian and breast cancer risk.

Lu is a co-investigator on the study, which asks, “‘Are we doing something medically very helpful but making them miserable?’ I don’t think that’s the case, but it’s very important to get at those issues,” she said.

“I feel strongly that [predictive testing] is empowering information for families. It helps me as a physician guide them better in terms of medical decision making,” Lu added.

—Cori Vanchieri