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SURGERY *or* Surveillance?

BRCA Mutation Carriers Weigh Their Options

By Karen L. Brooks

STORY SUMMARY

- Mutations in the genes BRCA1 and BRCA2 sharply increase the risk of breast and ovarian cancers.
- About 70 percent of carriers opt to have their ovaries removed and up to 40 percent have their breasts removed to reduce cancer risk.
- A new study suggests that BRCA1 carriers should pursue ovary removal by age 35 and BRCA2 carriers by age 40, although some physicians hesitate to adopt such stringent rules.
- Surgery is a personal decision, and women must work with their health-care providers to determine their cancer risk and choose the best approach to prevention.

Last year, 37-year-old actress Angelina Jolie generated global headlines by revealing she'd had a double mastectomy to reduce her risk of breast cancer. Jolie, who carries a mutation in the BRCA1 gene and lost her mother to ovarian cancer in 2007, again made news this spring when she announced plans for another cancer-prevention surgery: removal of her ovaries.

Physicians around the world reported seeing an immediate "Jolie Effect" after the star publicized her medical situation. Many women, particularly young ones, developed a sudden interest in genetic testing and became inspired to learn more about options for controlling their own cancer risks.

Preventing cancer through surgery is not a new phenomenon; for years, physicians have advised BRCA1 and 2 mutation carriers to consider prophylactic mastectomies and oophorectomies, or removal of the ovaries. About 70 percent of women who learn they have the mutations opt to have an oophorectomy, and up to 40 percent have a mastectomy. But these procedures are not right for every woman.

Massimo Cristofanilli, MD, director of the Jefferson Breast Care Center, says that while an increase in awareness of genetic counseling is a good thing, the downside to publicity is that patients sometimes act out of fear and make uninformed decisions.

"Since Angelina Jolie's story, all women want to know if they have BRCA mutations. The media can confuse them by imparting so much information about a role model doing something so drastic. Surgery is a very personal decision, and we must help each patient properly assess her risk and approach cancer prevention in the way that is most appropriate," Cristofanilli says.

BRCA Genes: What Are They?

BRCA1 and 2 genes (BReast CAncer genes 1 and 2) are inherited mutations that significantly increase a woman's risk of developing breast and ovarian cancer. According to the National Cancer Institute, these mutations account for 5 to 10 percent of breast cancers and 15 percent of ovarian cancers.

The NCI says that fewer than 2 percent of all women develop ovarian cancer during their lifetimes, but 39 percent of BRCA1 carriers and up to 17 percent of BRCA2 carriers do. About 12 percent of women develop breast cancer, but a BRCA mutation raises the risk four- to fivefold.

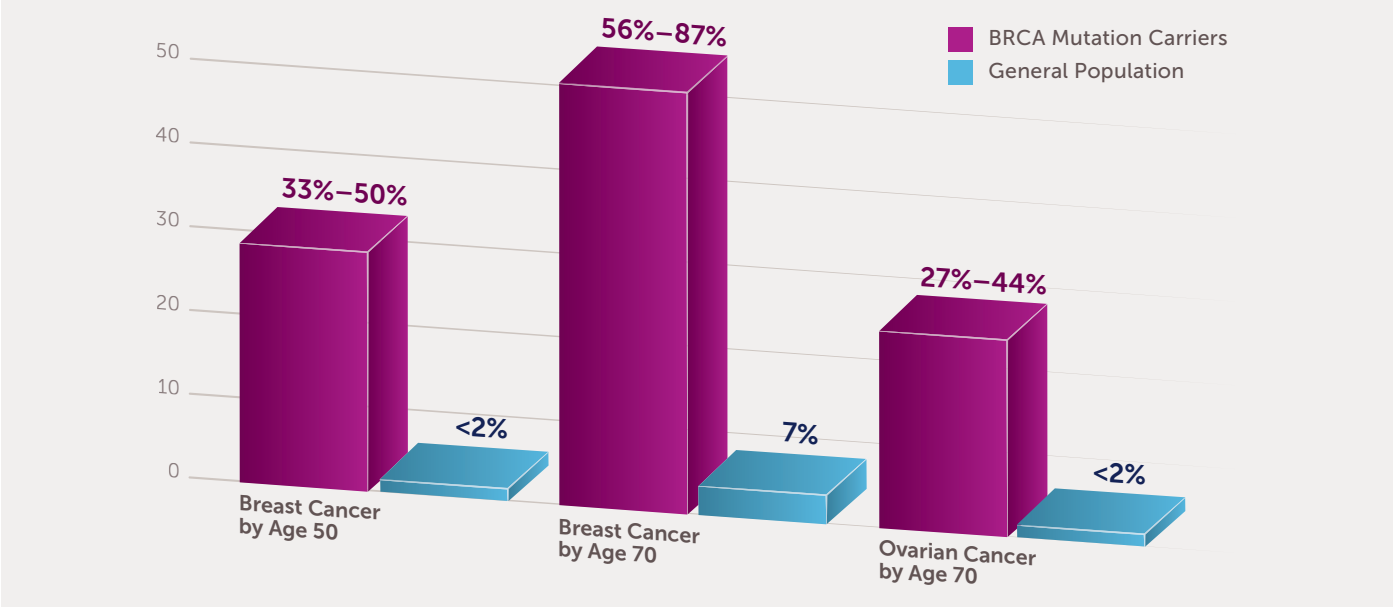
Past studies have shown removal of the ovaries and fallopian tubes in premenopausal women with BRCA mutations lowers risk for ovarian cancer by up to 95 percent and breast cancer by up to 60 percent, since the ovaries produce hormones that drive breast tumor growth. Ovarian cancer is especially deadly, and there is no reliable method for early detection like there is for breast cancer — so physicians often recommend that women with a BRCA1 mutation, which generally leads to cancer at a younger age, have their ovaries removed as soon as they are finished having children.

New Recommendations for Surgery

A Canadian study released in February 2014 was the largest ever to capture the protective powers of ovarian removal for BRCA1 and 2 mutation carriers and the first to break down different recommendations for each gene. Overall, researchers found that women who had oophorectomies reduced their risk of ovarian cancer by 80 percent and their risk of death before age 70 from any cause by 77 percent.

In the study, oophorectomy benefits varied based on the gene involved. BRCA1 carriers got the clearest advantage if surgery was performed by age 35, reducing their lifetime cancer risk

BRCA Mutation Increases the Risk of Cancer



to about 1 percent — similar to women without mutations. The findings revealed no ovarian cancers in BRCA2 carriers under 40, suggesting those women can safely delay surgery an extra five years.

Current guidelines from the American College of Obstetrics and Gynecology recommend prophylactic oophorectomy for both BRCA1 and 2 carriers by age 40, but the study's authors are pushing for 35 or younger to become the new universal standard for the procedure in BRCA1 carriers. Some physicians are hesitant to adopt such rigid guidelines.

"It is extremely difficult to agree on a strict recommendation for age regarding this procedure," Cristofanilli says. "Yes, there is an indication that a BRCA1 mutation can cause cancer earlier, and these women need to think about ovarian removal as a preventive measure. But there are so many factors that must be considered, especially family history and family planning. In certain cases, it is appropriate to delay surgery as much as possible. A hard rule of ages 35 and 40 — I don't know that it is right for everyone."

Theodore N. Tsangaris, MD, surgical director at the Jefferson Breast Care Center, agrees, explaining that the findings could frighten women into acting before they're ready.

"Everyone has different takes on the information that's given to them, and no matter what procedure you're talking about — oophorectomy or mastectomy — the optimal timing has to be determined individually. Neither of these surgeries can be undertaken without significant compromises that patients have to consider, even though we do know they are very effective and result in a very low risk of cancer," Tsangaris says. Bilateral mastectomy, which was not examined in the Canadian study, has previously been shown to reduce breast cancer risk by 95 percent in women with BRCA1 and 2 mutations.

As with all major surgeries, prophylactic mastectomy and oophorectomy carry potential complications such as bleeding and infection. Many women have babies through their late 30s, and ovary removal sends patients into abrupt menopause with symptoms that can be severe. The risk of bone-thinning osteoporosis also increases, although it can be controlled through diet, exercise and supplements. Breast removal can cause anxiety by affecting a woman's body image.

A Look at the Genes that Raise the Risk of Breast and Ovarian Cancer

- BRCA1 and BRCA2 mutations are uncommon (occurring in 1 of every 300 to 800 women, according to the American College of Obstetricians and Gynecologists) but are thought to account for 5 to 10 percent of all breast cancers and about 15 percent of ovarian cancers.
- If multiple family members have had breast or ovarian cancer, particularly at a young age, the U.S. Preventive Services Task Force says a woman should discuss with a health professional if she's at increased risk. A genetic counselor can help her decide whether to have a blood test to see if she inherited faulty genes.
- Physicians advise women with BRCA mutations to undergo frequent screenings for breast cancer and to consider having their ovaries removed between ages 35 and 40 or when childbearing is complete (recent research suggests BRCA1 carriers should pursue surgery at the earlier age).

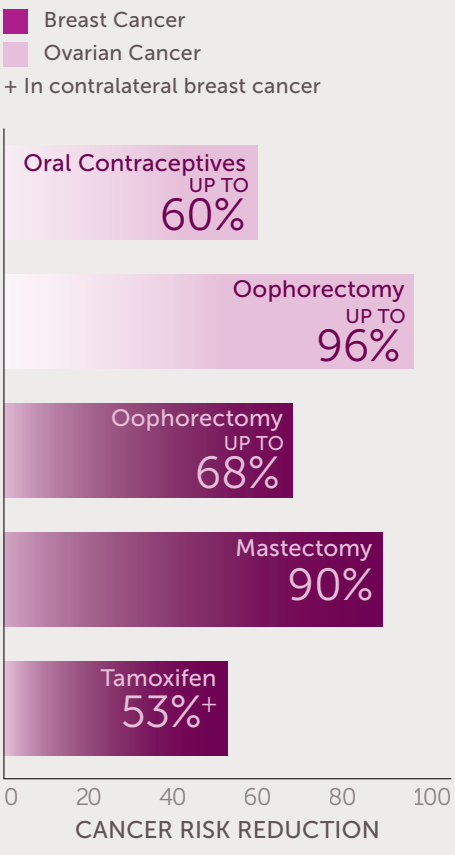
Regardless of these drawbacks, says Jefferson breast surgeon Melissa A. Lazar, MD '06, the majority of BRCA mutation carriers are eager to move forward with prophylactic surgery. "Most women who carry mutations have seen relatives experience cancer. They've seen loved ones go through treatments like chemotherapy and have probably seen some pass away from the disease. I think their fear of developing cancer outweighs some of the negatives of surgery, and providing patients with resources for psychological support is important," Lazar says.

Alternatives to Surgery

For mutation carriers who are strongly opposed to having surgery, other preventive measures can be taken. Drugs like tamoxifen can cut a woman's risk of breast cancer by up to half, as can ordinary oral contraceptives.

Proactive Cancer Management Reduces the Risk

PREVENTIVE MEASURES



"Tamoxifen is certainly something to consider for breast cancer prevention, but you don't know how many years you'll stay on it. This can turn into a lifelong treatment with a drug that has side effects. And if a patient is of reproductive age, she cannot have children while taking tamoxifen," Cristofanilli says. For postmenopausal women, the drug raloxifene is another option for cutting breast cancer risk.

Any BRCA mutation carrier who does not want to undergo a mastectomy should be closely monitored with frequent screenings.

"If someone is a carrier but doesn't want to have surgery, she should have annual mammography and annual MRI, and we like to stagger it so she's getting some form of imaging every six months," Lazar says. "The National Comprehensive Cancer Network also recommends breast awareness starting at age 18 and a clinical breast exam every six to 12 months."

Unfortunately, there are no reliable methods for early detection of ovarian cancer.

"We do know of some markers, but there has not been success in developing a screening test," Cristofanilli says. "Women with a BRCA mutation do have to plan their families earlier rather than later and be prepared to make a major decision regarding ovary removal at a relatively young age."

Jefferson Eyes New High-Risk Clinic

Tsangaris says faculty members at Jefferson aim to establish a special service for women who have a high cancer risk, whether due to a BRCA mutation, strong family history or other factors. Currently, he says, most services force these patients to get their information piecemeal.

"First, a woman might talk to the geneticist. And then, depending on what the geneticist tells her, she's faced with some major decisions. If she's genetically positive but doesn't have cancer, what should she do? Increase her screening? Take a preventive like tamoxifen? Or go ahead and have surgery?" Tsangaris says. "We want to take away the confusion by creating a comprehensive clinic where women can get all the information they need from the appropriate experts—geneticists, oncologists, surgeons — in a streamlined way and then make intelligent decisions that are right for them."

Key to the clinic's success, he says, will be a full-time coordinator who will manage patients' experiences from genetic testing to screening to prophylactic or therapeutic treatment.

"What Angelina Jolie did is not right for every woman, and after the Jolie Effect, you need to help women put their risk in perspective. This is one of the top specialty clinics we'd like to offer, and we are currently looking for philanthropic investments to support it. Nobody else in our area is bringing coordinated, high-risk cancer care together like this, and women deserve clear information to determine what course of action makes the most sense." ■

For more information about plans for a high-risk cancer service or to support the initiative, contact Paul Gunther, Director of Development for Oncology, at paul.gunther@jefferson.edu or 215-955-9446.

What is Hereditary Breast Ovarian Cancer (HBOC) Syndrome?

HBOC is caused by BRCA1 and 2 gene mutations and is characterized by the following features in a family:

- Early age of onset of breast cancer (often before age 50)
- Family history of breast and ovarian cancer
- Increased chance of bilateral cancers (cancer that develop in both breasts, or both ovaries, independently) or an individual with both breast and ovarian cancer
- An autosomal dominant pattern of inheritance (vertical transmission through either the mother or father's side)
- An increased incidence of tumors of other specific organs, such as the prostate

Other factors that increase the chance that a family has HBOC syndrome include:

- Family history of male breast cancer
- Ashkenazi Jewish ancestry