BRCA1/2: Why Men Should Be Screened for the “Breast Cancer Gene”

Men who carry mutations in the BRCA1 and BRCA2 genes can see increased risk of several cancers. New guidelines help educate patients.

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They are genes commonly associated with breast cancer in women, but in fact men who carry certain mutations in their BRCA1 or BRCA2 genes are at higher risk of developing certain types of cancer themselves.

These risks for men traditionally have been under-recognized, but newly developed national screening guidelines offer hope for identifying the cancer risk of BRCA mutations in men through genetic testing and tailored cancer screening, according to an article published July 25 from Fred Hutch Cancer Center and University of Washington scientists in the journal JAMA Oncology.

The article reviews the most recent screening and treatment guidelines for men carrying an inherited damaging variant in two genes, BRCA1 and BRCA2, known to significantly increase the risk of breast cancer and ovarian cancers in women. The review includes updated recommendations for males with a family history of cancer and other risk factors that could help them, and their doctors, understand cancer risks.

Identification of these genetic risks can lead to tailored screening, finding cancers earlier and thus improve their chances for better cancer treatment outcomes. Male carriers of BRCA1/2 mutations are at higher risk of prostate, pancreatic, breast and other cancers over the course of their lifetimes.

Heather Cheng, MD, PhD, the director of the Fred Hutch Prostate Cancer Genetics Clinic, led the study. Fred Hutch cancer physician and researcher Daniel Lin, MD, contributed to the paper, along with University of Washington School of Medicine professors Mary-Claire King, PhD, and Colin Pritchard, MD, PhD, in tandem with a team of experts from other institutions.

For the purposes of the study, the term “males” applies to individuals assigned male sex at birth, regardless of gender identity. The study authors stress that all patients should work with their primary care providers to obtain appropriate individualized cancer screening based on sex-specific organs.

Cheng described awareness of male cancer risks for BRCA1 or BRCA2 mutation carriers as an unmet need not only among males, but also the medical community.

“Not enough men are getting genetic testing to see if they carry a BRCA1 or BRCA2 gene variant that increases their cancer risk,” Cheng said. “And the men who know they are carriers get tested for their daughters, but don’t always know why it’s important for their own health.”

Cheng stressed the need for males to be aware of their family history of cancer and to share this important information with their primary care providers throughout their lives.

BRCA: Not just a breast cancer gene

The link between the BRCA1 gene and breast cancer was discovered in 1990 by King, a professor of medical genetics and genome sciences at the University of Washington. Although the healthy version of the gene has no impact on breast cancer, King named the gene after “BReast CAncer” for the increased risk of cancer conferred by specific disease-causing variants of the gene, according to the National Breast Cancer Foundation.

Later work led to the identification of a related gene, BRCA2. Together, these genes help maintain the accuracy of cellular DNA during cell division.

The BRCA1 and BRCA2 genes are involved in repairing what is known as double-stranded DNA breaks: a full break in both strands of DNA. When BRCA1 and BRCA2 are working properly, cell division pauses until double-stranded DNA breaks have been repaired.

“BRCA1 and BRCA2 are members of a family of genes involved in maintaining high quality and ensuring correct and uncorrupted copies of the DNA instructions,” Cheng said.

Normally-functioning BRCA1 and BRCA2 genes help the cell to repair the DNA before it is passed on to daughter cells every time a cell divides. The loss of function of this proofreading mechanism can lead to uncontrolled cell division and tumor development, the hallmarks of cancer.

Together, mutations in BRCA1 or BRCA2 account for significantly increased risks for both breast and ovarian cancer in female carriers, though the risks for each type of cancer are different depending on multiple factors, including the specific gene mutation carried.

Up to 72% of women with a BRCA1 or BRCA2 mutation develop breast cancer by 70–80 years of age. Less well known is the increase in ovarian cancer risk: up to 44% of female BRCA1/2 mutation carriers develop ovarian cancer compared with 13% for breast cancer and 1.2% for ovarian cancer in the general population, according to the National Cancer Institute, or NCI.

Increased awareness of the risks associated with BRCA1/2 has led to the development of many options for risk reduction and early cancer screening for women.

Far less well known, however, is the fact that biological males account for a full 50% of the

population of people who carry a BRCA1 or BRCA2 mutation. The cancer risk to them and their families extends beyond the risk of their daughters inheriting the mutation.

Men with BRCA1 or BRCA2 mutations have statistically significant increased risk of several types of cancer.

Carrying a BRCA1 or BRCA2 mutation confers up to an 8.6-fold increased risk of developing prostate cancer, and up to an absolute lifetime risk of 60%.

For pancreatic cancer, the presence of BRCA1/2 mutation is implicated in up to a 7.8-fold increase in the risk of developing cancer, with the risk increasing significantly after age 50.

Male breast cancer risk also increases for BRCA1/2 mutation carriers, with the risk of developing this otherwise relatively rare disease increasing to 7–9% from less than 0.02% in the general population.

In addition to prostate, pancreatic and breast cancer, male BRCA1 or BRCA2 carriers may also have an increased risk of other cancers, such as gastrointestinal cancers and melanoma, depending on their family history of cancer.

An unmet need: Education, awareness and screening for men

Despite the increased cancer risk for BRCA1 or BRCA2-carrying males, national guidelines on genetic testing and cancer screening have been slower to emerge for males, and national guidelines are now beginning to include more specific measures for males.

With less public awareness of the risk for males carrying BRCA1 or BRCA2 mutations, physicians and other health care professionals may not always be aware of the most up-to-date screening recommendations, which may exist in different places.

National organizations such as the NCI have been slow to recognize the importance of linking prostate cancer risk to the BRCA gene in public-facing health education materials. The current study aimed to bridge this knowledge gap by aggregating and summarizing screening and treatment guidelines from several major public health organizations to provide a road map for patients and their doctors in assessing their cancer risk.

Physicians can help bridge the knowledge gap by encouraging their male patients to learn about their own family history with cancer, which can lead to the identification of risk factors and a recommendation for genetic testing.

Women traditionally have been more proactive about preventive care because they are more likely to see a physician for routine cancer screenings such as those for cervical and breast cancer earlier in their lives. However, Cheng stressed that men should become more proactive about knowing their family history of cancer and asking their primary care physician about the possibility

of genetic testing as well.

“Half of the people who carry BRCA1 and BRCA2 mutations are males and may not know about it,” Cheng said. “Angelina Jolie talked very openly about her status as a BRCA carrier, and I think that really raised awareness for women. Men carry the same genes, and they are also at risk for a different set of cancers. There are ways to find cancer earlier, including PSA, prostate specific antigen, blood tests at a younger age, as well as clinical screening trials.”

Understanding clinical genetic testing

Confusion about the many different types of DNA testing available to the public today presents another challenge for males being tested for the BRCA1 and BRCA2 mutations.

Popular direct-to-consumer services, such as 23andMe and Ancestry, perform some genetic testing using DNA collected from saliva, but these services are not adequate for identifying the genetic variants most likely to increase cancer risks.

The most accurate type of genetic testing for medical purposes should be done via a saliva or blood test performed under the supervision of a genetics specialist or medical provider.

Genetic testing should be performed with access to appropriate genetic counseling services delivered by a certified professional genetic counselor so that patients understand the test’s findings and implications for their health and if they have children, for the health of their children.

Insurance coverage for genetic screening is improving, Cheng noted, with costs decreasing over time. Medical privacy laws, such as the Genetic Information Nondiscrimination Act (GINA) of 2008, protect Americans from employment and health insurance discrimination based on the results of genetic testing, but other factors such as long-term care and life insurance could be impacted.

Cheng said that patients should ensure they are comfortable with the information and options before testing, and are encouraged to consult a genetics specialist if they have more questions or concerns.

After genetic testing: More choices for prevention and early detection for patients and their families

Men whose genetic tests indicate a BRCA1 or BRCA2 mutation have many more options today for proactive early cancer detection and more effective cancer treatments such as PARP inhibitors.

Because genes are inherited from generation to generation, there is a fifty percent chance that a male carrier of a BRCA1 or BRCA2 mutation shares this mutated gene with their biological offspring. The earlier people are aware of the possibility of carrying a BRCA1 or BRCA2 mutation, the more their medical care can be personalized and tailored to their specific situation: a hallmark

of the promise of personalized medicine.

Cheng, who treats prostate cancer patients at the South Lake Union clinic at Fred Hutch, noted that programs such as the Fred Hutch Prostate Cancer Genetics Clinic, the Gastrointestinal Cancer Prevention Program and the Breast and Ovarian Cancer Prevention Clinic collaborate to provide comprehensive resources for both patients with cancer and their family members who may also carry increased inherited cancer risk.

“We have multiple programs centered around cancer genetics and prevention that help patients and their families,” Cheng said. “I get to meet the brothers and sons of my patients, some before they have cancer, in order to talk about screening for prostate cancer. And that’s really gratifying. It’s important for folks out there to know that we have these resources because sometimes they don’t know where to go for state-of-the art cancer early detection, prevention and treatment.”

A call to action for men at risk

Cheng and her team identified two clear calls to action for men and their primary care physicians.

1. More men should be offered genetic screening for these potential cancer-causing mutations. The current rate of testing for men is only one-tenth of the rate for women, even though male carriers of BRCA1 or BRCA2 mutations have a significantly higher lifetime risk of developing cancer.
2. Awareness of this issue needs to increase among medical professions and the public.

National guidelines for males who carry a BRCA1 or BRCA2 mutation are available at BRCA Research and Cure Alliance and Basser Center for BRCA.

Men should become more proactive about discussing their families’ cancer history with their physician to ensure that they are given access to genetic testing where needed.

For men who have a specific family cancer history but are unsure of where to turn, Cheng recommended speaking with a primary care provider or genetics expert to assess whether genetic testing might be a helpful first step.

Taken together, these actions should help more men understand their lifetime cancer risk, which can lead to earlier cancer detection and better outcomes.

It will also help researchers to expand their knowledge of these diseases by learning about how these cancers affect men from different ethnicities and backgrounds, leading to an improved understanding of cancer-causing genes and how they can be treated with new interventions.

“These are recent guideline changes,” Cheng stressed. “I personally hope that as more people, including males [are screened], we can advance progress and research faster, find the people most impacted and work together to reduce the burden of BRCA1 and BRCA2-related cancers.”

All told, the most important takeaway is a simple one, Cheng said: “It affects men too.”

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