Genetic susceptibility for breast and ovarian cancer
Screening, prevention and fertility preservation

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Each year, approximately 20 out of 100,000 America women die from breast cancer and seven out of 100,000 will die of ovarian cancer.[1] Breast cancer remains one of the most common cancers among women, and the rate of new breast cancer diagnoses is rising.[2,3] Ovarian cancer accounts for about 5% of all cancer deaths among women, more than any other cancers of the reproductive system.[4]

Most breast cancer cases are caused by environmental or lifestyle factors such as lack of physical activity, poor diet, being overweight or obesity, frequent drinking of alcohol, chest radiation, or hormone replacement therapy. Of women with breast cancer, less than 15% have a first-degree relative with breast cancer and only about one percent will be positive for BRCA1 or BRCA2 gene mutations.[5] For ovarian cancer, the most important risk factors aside from age are strong family history of breast or ovarian cancer.[4] For both breast and ovarian cancer, inherited gene mutations, such as BRCA1 or BRCA2, can increase risk.[4]

Women with a genetic mutation have been called "cancer previvors"—survivors of a predisposition to cancer, though they currently do not have the disease.[6] Not all women who have a family history will carry an identifiable gene mutation.[5] Those who have BRCA1 and BRCA2 gene mutations can have an increased lifetime risk of developing breast cancer by approximately 65% to 80% and ovarian cancer by 20% to 40%.[7] These gene mutations also increase the risk for cancers in the fallopian tubes and peritoneum.[8]

Among women at increased genetic risk, appropriate screening, testing and preventive strategies are critical to managing overall health and any potential concerns about future fertility.

Screening and counseling

The U.S. Preventive Services Task Force recommends screening for women with a family history of breast, ovarian, fallopian tube or peritoneal cancer.[9] During screening, a physician may assess the personal health history and the health history for up to three generations of paternal and maternal family lineages.[5]

Such screening should also include genetic counseling to determine whether testing for BRCA and other genes associated with the increased risk of breast cancer would be helpful. However, given the cost of genetic testing and the anxiety it can provoke, the Task Force discourages routine genetic testing for BRCA mutations among women whose family history is not associated with an increased risk of BRCA mutations.[9]

Prior to any testing, genetic counseling is critical to helping a patient understand the emotional and medical implications of genetic testing. This can help patients manage the decision-making process if they receive a positive result. Learning of a genetic disorder can cause patients to make life-altering choices. A primary care physician may not be equipped to counsel patients through such genetic evaluations. Expertise from a professionally trained genetic counselor might help patients make informed decisions voluntarily, in a nondirective manner.[10]

Genetic testing

Genetic testing typically relies on a cheek swab or blood sample. Two types of testing are available: A genetic test can identify a specific, known familial mutation. A genomic test can provide a comprehensive analysis of the sequence and expression of groups of genes, fragments of the genome or the whole genome.[5] Genetic test results vary depending on the specific gene involved, the level of increased risk and type of cancers that occur in the family.

- The BRCA1 and BRCA2 genes are high-penetrance genes, indicating a high likelihood of affecting individuals with the mutation.[5]
- If a BRCA1 or BRCA2 germline mutation is present, it will be in all cells of the body at conception, and can be passed on to future generations.[5]
- Women and men with BRCA1 or BRCA2 mutations are at increased risk for breast, fallopian tube and prostate cancer. These mutations also account for 15% of ovarian cancers.[5] Other mutations, such as PTEN, TP53, STK11, CDH1, RAD51C, RAD51D and PALB2, also increase the risk of breast cancer, but to a lesser degree than BRCA1 or BRCA2.[8,11]

The National Comprehensive Cancer Network published guidelines on genetic/familial high-risk assessment in breast and ovarian cancer for multigene testing in 2017.[12] Patients who already have cancer should undergo genetic testing early, as decisions for more aggressive treatment may be warranted.[5] As the cost of genetic testing continues to fall, and genetic variation is detected with higher accuracy, genetic testing technology will increasingly influence and alter clinical decisions.[8]

Prevention strategies

Genetic testing is helpful where there are opportunities for prevention. There are a number of prevention strategies for those with a new diagnosis of breast and gynecologic cancer who test positive for genetic susceptibility:

- Increased surveillance with breast MRI, annual mammography and semiannual clinical breast exams
- Surgical interventions including bilateral total mastectomy to reduce breast cancer risk in high-risk women by 90%[13]
- Bilateral oophorectomy to eliminate the body's main source of estrogen and reduce the risk of breast cancer in BRCA2 carriers by 72%[13]
- Precancer BRCA-tailored treatment strategies, including poly (ADP-ribose) polymerase (PARP) inhibitors, platinum salts and chemoprevention[7]; in particular, adjuvant therapy with tamoxifen, which has been shown to halve the risk of developing breast cancer in patients with germline BRCA1 or BRCA1 mutations[8]
- Genetic testing in newly diagnosed patients to help guide treatment decisions, as women with BRCA mutations have poorer prognoses and a higher likelihood of disease recurrence, and BRCA1 mutations are associated with triple negative breast cancer[5]

Nurses are instrumental in educating patients about prevention strategies. Treatment goals include finding a particular cancer's vulnerabilities and identifying available therapy or clinical trials that will benefit the patient the most.[8]

Fertility challenges

Several studies have found links between BRCA genetic susceptibility and reduced fertility.[14] A number of studies suggest that occult ovarian insufficiency, a syndrome of infertility, regular menses and elevated follicle stimulating hormone (FSH) concentrations, might affect those with BRCA mutations:

- During in vitro fertilization (IVF), fewer eggs were retrieved from women with the BRCA1 mutation. The low response rate was not seen in patients with the BRCA2 mutation.[15]
- BRCA carriers consistently trended toward higher gonadotropin doses, lower anti-mullerian hormone (AMH) levels, lower number of retrieved oocytes and a higher rate of low ovarian response (less than four oocytes), further substantiating an association between BRCA mutations and low ovarian reserves, alongside lower response rates to stimulation.[7]
- Menopause came earlier for women carrying the BRCA mutations.[16]

Additionally, male BRCA2 carriers often have altered sperm production.[7,17] Given the bulk of research findings, BRCA mutation carriers should be counseled to consult a fertility specialist who can assess their ovarian reserve with an AMH measurement and antral follicle count. Based on the results of these tests, BRCA carriers might be advised not to delay pregnancy.[7]

Preimplantation genetic testing and IVF

Women who carry a genetic susceptibility to breast cancer are confronted with the knowledge that they could pass the genetic mutations to the next generation. Research shows that BRCA carriers have a 50% chance of passing genetic mutations to their future children.[18] Preimplantation genetic testing for monogenic disorders (PGT-M), previously called preimplantation genetic diagnosis (PGD), is a form of genetic analysis that allows mutation carriers to eliminate the 50% risk that offspring could inherit a BRCA mutation.[18]

PGT-M begins with ovarian stimulation, which uses medication to help a woman produce multiple eggs for retrieval via outpatient procedure. The eggs undergo IVF in a lab, where they progress to the embryo stage. One to two cells are removed from an embryo and tested for BRCA mutations.

Once test results are available, embryos free of the BRCA mutation may be transferred to a patient's uterus or cryopreserved for her future use.[18,19]

However, a 2019 study found several reasons patients did not pursue PGT-M: cost (38.8%), completed childbearing (25%), medical risk (18.8%) and ethical concerns (16.2%).[20] Some have also expressed concern that IVF ovarian stimulation protocols, which induce an increased estrogen environment, might put BRCA mutation carriers at greater risk for developing cancer. The concern has caused patients to complete IVF cycles without ovarian stimulation. However, this practice yields a less favorable embryo and pregnancy rate.

Several sources state that infertility treatment and fertility medications do not seem to adversely affect the risk of breast cancer for current patients or BRCA mutation carriers.[7] Studies of modified regimens, which use tamoxifen, letrozole or a combination of these medications with mild gonadotropin stimulation for embryo cryopreservation, suggest likewise.

One study compared breast cancer patients receiving letrozole during fertility preservation treatment with a control group of breast cancer patients receiving no fertility-preserving measures. The study found a hazard ratio for cancer recurrence after ovarian stimulation of 0.77, and survival was not compromised compared to controls. Upon follow-up several years after treatment, there were six occurrences in the fertility preservation group and 12 in the control group.[21]

Another study concluded that a letrozole and FSH protocol appeared to be a preferable approach when there is concern about high estradiol levels.[22] Another recent study did not find an increased risk of ovarian cancer for either BRCA1 or BRCA2 carriers when hormones were given during IVF.[14] However, research is ongoing, and patients are encouraged to discuss their options with their clinical team.

It is also important to note that many cycles of IVF and PGT may be needed to get embryos without BRCA mutations and to achieve pregnancy. Each cycle can cost approximately $10,000 to $20,000, and cost estimates for PGT can range anywhere from $500 to $120,000.[20] Health insurance might offer some coverage, but multiple cycles can be costly.[18] Clinicians should help patients learn about the PGT-M and IVF processes to make informed decisions for themselves and their families.[20]

Ethical considerations

In addition to medical, emotional and financial concerns, many ethical considerations are part of navigating a genetic susceptibility for cancer. Couples who want to prevent passing on a gene mutation might face ethical dilemmas about discarding embryos that carry the mutation during IVF with PGT-M. Others might grapple with the decision of terminating a pregnancy of a healthy fetus that is carrying a potential for adult onset cancer when there is no guarantee the child will or will *not* develop cancer or another serious disease in their lifetime. There is also some ethical concern regarding the fact that many women undergoing chemotherapy for breast cancer or bilateral salpingo-oophorectomy to reduce their cancer risk are not given the option of PGT-M and embryo freezing prior to initiation of these treatments.[7]

Those aware of their carrier status might restrict life plans by not marrying, not having children or not making certain career choices, which can lead to frustration and isolation. With the availability of direct-to-consumer genetic testing, women of reproductive age might have access to knowledge about their mutation status that could lead to them to choose not to have children.[23] Because BRCA mutations are not a disease, it is possible that carriers could find ways to reduce risk later in life, and might have access to future advancements to manage their risk or even prevent a future diagnosis.[18] Some argue that *not* knowing whether you are a BRCA mutation carrier could result in a happier, normal life.[10] With ever increasing scientific discovery, BRCA mutation carriers have more options than ever before when making decisions about their health, their fertility and potentially the health of future generations.

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About the author

Jean Cherry, BSN, MBA, is a clinical manager for the Walgreens Clinical Programs and Quality Department. Cherry began her nursing career specializing in telemetry, cardiovascular surgery and heart transplantation. She became a research coordinator for the International Diabetes Center and later a disease management product director for Optum. Cherry has presented poster abstracts on quality measures at conferences for the United Network for Organ Sharing and Children's Hospital of Philadelphia. She has also served on the board of directors for Avinity Senior Living. Cherry holds a Bachelor of Science in nursing from the UND and a Master of Business Administration from Bethel University.

References

1. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, published June 2019. Accessed October 9, 2019.
2. Centers for Disease Control and Prevention. Breast Cancer Statistics. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/cancer/breast/statistics/index.htm. Updated May 28, 2019. Accessed July 26, 2019.
3. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016): U.S. Department of Health and Human Services, CDC and National Cancer Institute. www.cdc.gov/cancer/dataviz. Accessed July 26, 2019.
4. American Cancer Society. Cancer Facts and Figures 2019. American Cancer Society Web site. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed September 18, 2019.
5. Lynch JA, Venne V, Berse B. Genetic tests to identify risk for breast cancer. *Semin Oncol Nurs*. 2015;31(2):100-107.
6. Facing our Risk of Cancer Empowered (FORCE). *Cancer previvors*. FORCE Web site. https://www.facingourrisk.org/understanding-brca-and-hboc/information/previvors-survivors/cancer-previvors/. Updated December 29, 2016. Accessed August 1, 2019.
7. Daum H, Peretz T, Laufer N. BRCA mutations and reproduction. *Fertil Steril*. 2018;109(1):33-38.
8. Godet I, Gilkes DM. BRCA1 and BRCA2 mutations and treatment strategies for breast cancer. *Integr Cancer Sci Ther*. 201;4(1):10.1576/ICST.1000228.
9. U.S. Preventive Services Task Force. *Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women*. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing. Accessed October 9, 2019.
10. Fulda KG, Lykens K. Ethical issues in predictive genetic testing: a public health. *J Med Ethics*. 2006;32(3):143-147.
11. NCCN guidelines insights: Genetic/familial high-risk assessment: breast and ovarian Version 2.2017. *J Natl Compr Canc Netw*. 2017;15(1); 9-20. https://jnccn.org/view/journals/jnccn/15/1/article-p9.xml. Accessed July 30, 2019.
12. Moyer VA; U.S. Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(4):271-281.
13. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol*. 2008;26(8):1331-1337.
14. Gronwald J, Glass K, Rosen B, et al. Treatment of infertility does not increase the risk of ovarian cancer among women with BRCA1 or BRCA2 mutation. *Fertil Steril*. 2016;105(3):781-785.
15. Oktay K, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. *J Clin Oncol*. 2010;28(2):240-244.
16. Lin WT, Beattie M, Chen LM, et al. Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non-clinic based sample of women in northern California. *Cancer*. 2013;119(9):1652-1659.
17. Pal T, Keefe D, Sun P, Narod SA; Hereditary Breast Cancer Clinical Study Group. Fertility in women with BRCA mutations: a case-control study. *Fertil Steril*. 2010;93(6):1805-1808.
18. Preimplantation genetic diagnosis for BRCA mutation carriers. Breastcancer.org Web site. https://www.breastcancer.org/symptoms/testing/genetic/preimplantation-genetic-diag. Updated April 25, 2016. Accessed July 30, 2019.
19. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. *Hum Reprod*. 2017;32(9):1786-1801.
20. Khouri OR, Gerber D, Smith JA, Boyd LR. Preimplantation genetic diagnosis: What do BRCA mutation carriers think? *J Clin Oncol*. 2019;37(15_suppl):1526.
21. Kim J, Turan V, Oktay K. Long-term safety of letrozole and gonadotropin stimulation for fertility preservation in women with breast cancer. *J Clin Endocrinol Metab*. 2016;101(4):1364–1371.
22. Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J Clin Oncol*. 2005;23(19):4347–4353.
23. Smith KR, Hanson HA, Hollingshaus MS. BRCA1 and BRCA2 mutations and female fertility. *Curr Opin Obstet Gynecol*. 2013;25(3): 207-213.