BRCA and beyond: The contribution of genetics to breast and gynecologic cancers (Part 1)

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Faculty
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Intended audience
This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners who provide care for women in any age bracket.

CE approval period
Now through September 30, 2018

Estimated time to complete this activity
1 hour

CE approval hours
1.0 contact hour of CE credit

Needs assessment
This two-part article focuses on hereditary cancer syndromes associated with breast and gynecologic cancers. In part 1, the author provides background information about hereditary cancer, details several specific hereditary breast and gynecologic cancer syndromes (HBGCSs), and explains the gene alterations involved in these syndromes. In part 2, the author will describe ways that healthcare providers can identify women who may have one of these syndromes and who could therefore benefit from genetic risk assessment, counseling, and testing—processes she also discusses. The author will also explain how to interpret genetic test results and provide management recommendations for the two most common HBGCSs.

Educational objectives
At the conclusion of this educational activity, participants should be able to:
1. Know the proportion of cancers that are hereditary, as compared with those that are sporadic or familial.
2. Recognize genes that may have pathogenic variants that can cause an HBGCS.
3. Understand the distinguishing characteristics of several different HBGCSs.

Accreditation statement
This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women’s Health (NPWH), and has been approved for 1.0 contact hour of CE credit.

Faculty disclosures
NPWH policy requires all faculty to disclose any affiliation or relationship with a commercial interest that may cause a potential, real, or apparent conflict of interest with the content of a CE program. NPWH does not imply that the affiliation or relationship will affect the content of the CE program. Disclosure provides participants with information that may be important to their evaluation of an activity. Faculty are also asked to identify any unlabeled/unapproved uses of drugs or devices made in their presentation.

Kate McReynolds, APRN, MSc, MSN, ANP-BC, AGN-BC, has no actual or potential conflicts of interest in relation to this presentation.

Disclosure of unlabeled use
NPWH policy requires authors to disclose to participants when they are presenting information about unlabeled use of a commercial product or device or an investigational use of a drug or device not yet approved for any use.

Disclaimer
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Successful completion of the activity
Successful completion of this activity, J-17-03, requires par-
Cancer can be categorized as sporadic, familial, or hereditary.\(^1\) Sporadic cancers (70%-80% of cancer cases) occur by chance—for example, because of a mistake that occurs during cell division—or as a result of a lifestyle choice (e.g., smoking) or a toxic environmental exposure. Familial cancers (15%-20% of cases) are likely caused by a combination of genetic and environmental risk factors.\(^2\) Although persons with familial cancers may have several relatives with the same type of cancer, a clear pattern of inheritance has not been established. Hereditary cancers (5%-10% of cases) occur when a person has a specific altered (mutated) gene in nearly every cell in the body.\(^3\) Persons with hereditary cancers are more likely to have family members with the same type or a related type of cancer. They tend to develop cancer at an earlier-than-average age and may develop more than one cancer in their lifetime.

The following statistics put the three categories of cancer in perspective. With regard to breast cancer, about 12% of women in the general population will develop the disease in their lifetime.\(^4\) A woman's risk for developing breast cancer nearly doubles if she has a first-degree relative (mother, sister, daughter) with breast cancer.\(^5\) If genetic testing reveals that she has a BRCA1 mutation associated with hereditary breast and ovarian cancer (HBOC) syndrome, her risk for developing breast cancer may be as high as 72%.\(^6\) With regard to ovarian cancer, about 1.3% of women in the general population develop the disease.\(^7\) If a woman has a first-degree relative with ovarian cancer, her risk triples—to about 5%.\(^8\) If genetic testing reveals that she has a BRCA1 mutation, then her risk for developing ovarian cancer, according to data from the EMBRACE study, may be as high as 59%.\(^9\)

Part 1 of this article provides general information about hereditary breast and gynecologic cancer syndromes (HBGCSs) and describes specific HBGCSs that healthcare providers (HCPs) caring for women may encounter in their practices. In addition, the author discusses how and why these syndromes develop. Part 2 of this article, which will appear in the next issue of Women’s Healthcare: A Clinical Journal for NPs, focuses on when to suspect that an HBGCS may be present in a woman with a personal or family history of breast, ovarian, or other gynecologic cancer; when it is appropriate to test for pathogenic variants (i.e., mutations) in genes that may be responsible for a breast or a gynecologic cancer.
cancer; the implications that the findings, positive or negative, would have for a patient and her otherwise healthy female relatives; the types of genetic tests for the mutations associated with these syndromes that are available; and the implications of these test results—that is, how they should guide management.

Hereditary breast and gynecologic cancer syndromes

A hereditary cancer syndrome is a genetic predisposition to develop certain types of cancer that are caused by an inherited mutation (from either parent) in one or more genes and that may cause the early onset of these cancers. Many of these syndromes are caused by mutations in tumor suppressor genes that code for proteins that protect against cancer, although in some syndromes, the mutated genes may promote the growth of cancer cells. In most cases, these genetic mutations result in an increased cancer risk for multiple organs. This article reviews hereditary cancer syndromes that may lead to breast and/or gynecologic cancers, including HBOC syndrome, Lynch syndrome (LS), Li-Fraumeni syndrome (LFS), Peutz-Jeghers syndrome (PJS), and Cowden syndrome. A review of basic cancer genetics is available in the Box.

Hereditary breast and ovarian cancer syndrome

Most cases of HBOC syndrome are caused by mutations in BRCA1 or BRCA2, which may be inherited from the mother or the father. Only one copy of the mutation is needed for a woman to be at increased risk for developing cancer of the breast and/or ovary (autosomal dominant inheritance). About 1 in 40 Ashkenazi (Eastern European) Jews is born with a BRCA1 or a BRCA2 mutation, as compared with 1 in 300-500 persons in the general U.S. population. Ashkenazi Jews’ increased likelihood of carrying a BRCA1 or a BRCA2 mutation is related to the founder effect, which is the reduced genetic diversity resulting when a population is descended from a small number of colonizing ancestors.

For women with a BRCA1 or a BRCA2 mutation, the risk for developing breast cancer starts to increase when they reach their mid-20s. With regard to ovarian cancer, the risk starts to increase for women with a BRCA1 mutation when they reach their mid-30s and for those with a BRCA2 mutation in their 40s to early 50s, although the risk is greatest when women with a BRCA1 or a BRCA2 mutation are in their 50s or older.

Using the results of multiple studies, Petrucelli et al have summarized the risk for malignancy in individuals, both female and male, with a germline BRCA1/2 pathogenic

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**Box. Review of basic cancer genetics**

The nucleus is the structure in our cells that contains most of our genetic material (a small amount is found in the mitochondria). In humans, each nucleus has 23 pairs of chromosomes, which contain a total of about 20,000 genes. We have two copies of nearly all of our genes, one from each parent.

Each gene consists of a long piece of DNA that provides instructions for protein synthesis. These proteins are used for cell structure, metabolism, and communication. As long as there is no mistake or mutation in the DNA, the protein will have the correct form and ability to be used by the body. However, a mutation existing in a gene may prevent the protein from being made, or the protein will not be correctly formed and will therefore not be utilized. Most of the aforementioned 20,000 genes make proteins that are not connected to cancer development. However, a number of genes, called tumor suppressor genes, code for proteins that are protective against cancer.

For the purpose of this discussion, let us focus on a BRCA1 mutation associated with HBOC syndrome. BRCA1 is a tumor suppressor gene; the protein for which it codes protects against breast cancer, ovarian cancer, and pancreatic cancer in women. Women without BRCA1–associated HBOC syndrome have two normal copies of BRCA1 in nearly all their cells, including their breast tissue. A sporadic breast cancer occurs when, over the course of her life, a woman acquires a mutation in one copy of the BRCA1 gene in a breast cell from carcinogen exposure or from a mistake that occurred during cell division; this is the “first hit.” At this point, the second normal copy of the BRCA1 gene in this breast cell is still producing a protein that is protecting the cell from cancer. However, if the second copy of BRCA1 in this breast cell also acquires a mutation—the “second hit”—it may develop into a cancer because now both copies of the BRCA1 gene in the cell are incapable of producing the protective protein.

It usually takes a long time for a cell to acquire the two hits; sporadic cancer is typically a disease diagnosed in older age. By contrast, a woman born with a BRCA1 mutation in one of her two copies of this gene has a head start in terms of her risk for developing breast cancer, ovarian cancer, or pancreatic cancer. Each breast cell in her body already contains the first hit. A BRCA1 mutation carrier needs only to acquire the second hit in a breast cell in order to develop cancer, an event that could occur at a relatively young age. Therefore, many women with an inherited BRCA1 mutation develop premenopausal breast cancer.

A good point to remember is that all cancer is genetic—that is, of or related to aberrations in the genes—but not all cancer is hereditary.
variant (a germline mutation is one that can be transmitted to offspring) (Table). In terms of breast cancer in women, the risk is 46%-87% for those with a BRCA1 mutation and 38%-84% for those with a BRCA2 mutation. In terms of ovarian cancer, the risk is 39%-63% for women with a BRCA1 mutation and 16.5%-27% for those with a BRCA2 mutation.

In addition to colorectal cancer, Lynch syndrome predisposes women to certain gynecologic cancers. Pancreatic cancer risk is 0.5% in the general population, as compared with 1%-3% in women with a BRCA1 mutation and 2%-7% in those with a BRCA2 mutation. Women with a BRCA2 mutation may also be at increased risk for melanoma. Finally, a recent study showed that women with a BRCA1 mutation who had undergone a risk-reducing salpingo-oophorectomy (RRSO) without hysterectomy had a slightly higher risk of developing serous and/or serous-like endometrial carcinomas, but not endometroid endometrial carcinomas or sarcomas.

Most BRCA1- and BRCA2-related breast cancers are invasive ductal carcinomas, which are more likely to be of higher histologic grade than sporadic breast cancers. Triple-negative breast cancers are more common in BRCA1 mutation carriers than in women with sporadic breast cancer. By contrast, BRCA2-related breast cancers tend to be hormone receptor positive. Ovarian cancers related to BRCA1/2 mutations are usually serous adenocarcinomas. Compared with ovarian cancers in non-carriers, those in BRCA1/2 mutation carriers are also more likely to be high grade.

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trial cancer is 25%-60% and that for ovarian cancer is 4%-24%. Risks for gynecologic cancers in MSH6 and PMS2 mutation carriers are increased but to a lesser degree.\textsuperscript{22} LS accounts for most cases of hereditary uterine cancer and CRC, and is the second most common cause of inherited ovarian cancer (after HBOC).\textsuperscript{23} Other cancers associated with LS include urothelial cancer, central nervous system cancer, gastric cancer, small bowel cancer, sebaceous carcinoma, hepatobiliary tract cancer, and pancreatic cancer.\textsuperscript{18}

**Li-Fraumeni syndrome**

The population prevalence of this highly penetrant autosomal dominant syndrome is 1 in 5,000-20,000.\textsuperscript{24} Women who carry a germline mutation in the TERT gene associated with LFS have a lifetime risk for cancer of nearly 100%, including a breast cancer risk of up to 60%, which often occurs when they are in their 20s or 30s.\textsuperscript{25,26} Other core cancers associated with LFS are sarcomas (soft-tissue and bone), brain cancers, and adrenocortical carcinomas, although a variety of other cancers may occur.\textsuperscript{26} Gynecologic cancers associated with LFS include ovarian cancer and endometrial cancer. Women with LFS also have a significantly increased risk of developing multiple primary cancers.\textsuperscript{27}

**Peutz-Jehgers syndrome**

Estimates for the birth prevalence of this rare syndrome range widely, from 1 in 25,000 to 1 in 280,000.\textsuperscript{28} This autosomal dominant syndrome is caused by mutations in the STK11 gene and is characterized by hamartomatous polyps in the gastrointestinal (GI) tract, mucocutaneous pigmentation, and increased risk for cancer. PJS is associated with elevated lifetime risks for breast cancer (32%-54%), benign ovarian tumors (sex cord tumors with annular tubules; 21%), rare and aggressive adenoma malignum of the cervix (10%), and uterine cancer (9%). Persons with PJS are also at increased risk for cancers of the pancreas and lung.

**Cowden syndrome**

This autosomal dominant syndrome is caused by mutations in the PTEN gene.\textsuperscript{29} This syndrome has a population prevalence of 1 in 200,000.\textsuperscript{24} Pathognomonic skin lesions such as papillomatous papules on the face and mucous membranes are nearly always present by age 30, and hamartomatous and mixed GI polyps, which increase the risk for CRC, are seen frequently. Cowden syndrome carries high lifetime risks for breast cancer (up to 85%) and endometrial cancer (up to 28%)\textsuperscript{29} in addition to increased risks for colon cancer, thyroid cancer, renal cell carcinoma, and melanoma.

**Clinical implications**

Identifying individuals who may have a hereditary cancer syndrome is an important task for nurse practitioners.\textsuperscript{30} If a woman is found to have an HBGCS, then risk reduction and/or screening measures can be implemented to prevent cancer or find it at an early stage. In addition, relatives of patients with an HBGCS can be offered individualized and quantified assessment of their own cancer risk, as well as options for tailored screening and prevention strategies.\textsuperscript{31} In Part 2 of this article, readers will learn more about when to suspect that an HBGCS may be present in a woman who has a personal or family history of breast, ovarian, or other gynecologic cancer.
References

Web resource
A. npwh.org/courses/home/details/905

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