

Breast Cancer Screening in the High-risk Population

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ABSTRACT

The risk for developing breast cancer can be influenced by a number of critical factors. An individual's age, gender, personal and family health history, nutritional status, level of physical activity, environmental exposures, and substance use can significantly shift the recommended screening guidelines format from the general risk population to a high-risk population. It is essential for health-care providers to become proficient in obtaining a complete cancer genetic risk assessment to accurately identify those who may be at high risk. There are a number of

evidence-based risk models that can be utilized by providers to determine if an individual is indeed at a higher risk to develop breast cancer. In addition, there are evidence-based guidelines for breast cancer screening and possible recommendations for medical management/risk reduction that are appropriate to discuss for those high-risk individuals.

Key words: Breast cancer, genetics, high-risk population, screening

Introduction

Cancer is caused by certain changes to genes that control the way our cells function, especially how they grow and divide. Genetic changes that increase cancer risk can be inherited from our parents if the changes are present in the reproductive or germ cells (germline changes). Cancer-causing genetic changes can also be acquired during an individual's lifetime due to errors that may occur during cell division (somatic changes). Inherited genetic mutations play a major role in about 5%–10% of all cancers.^[1] It is

important to remember that not all individuals who have a genetic mutation will automatically develop a cancer.

Comprehensive cancer genetic risk assessment is a consultative service that includes clinical assessment, genetic testing when appropriate, and risk management recommendations delivered in the context of one or more genetic counseling sessions.^[2] The value of genetic counseling has been endorsed by several professional organizations including the American College of Medical Genetics and Genomics, American Society of Clinical

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Oncology, American Society of Human Genetics, International Society of Nurses in Genetics, National Society of Genetic Counselors, National Comprehensive Cancer Network (NCCN), Oncology Nursing Society, and the Society of Gynecologic Oncologists. The main purposes of a cancer genetic risk assessment are to collect and evaluate personal, medical, and family information, to identify high-risk individuals who could benefit from genetic testing, cancer risk reduction, or early detection strategies, and to improve the quantity and quality of life.^[3] Cancer genetic risk assessment counseling has developed into a specialized practice that incorporates the knowledge of genetics, oncology, and individual as well as family counseling skills that may be offered by health-care providers with this interdisciplinary training.^[4]

The foundation for completing a cancer genetic risk assessment is established through the process of data collection. Data points to be gathered include the following: a three-generation pedigree, individuals' past health history and current health status, history of their prior cancer screenings, lifestyle factors and environmental exposures, cultural and religious beliefs, and race/ethnicity. It is important to gather family history from both the maternal and paternal sides of the family. Attempt to clarify the type of cancers may have occurred in various family members and their age at diagnosis. Additional data collection points include psychosocial factors, an individual's motivation for seeking risk assessment and possible genetic testing, evaluating primary language, cognitive style, and their preference for learning style. Explore how an individual processes information and how they dealt with stress in the past. This may provide insight as to how they may handle receiving a diagnosis of a pathogenic genetic mutation. A physical examination will also be able to confirm the presence of any significant clinical features of a potential hereditary cancer syndrome.

The creation of a family pedigree, whether it is hand drawn or computer generated, enables the health-care provider to symbolically represent family members, their social and biologic relationships, and lines of descent. It is important to verify information that is entered into a pedigree and to confirm biologic relationships due to the clinical decisions that may be made based on the information. Table 1 lists the most common family members included in a three-generation pedigree and how they are connected to the individual receiving the cancer genetic risk assessment. The pedigree often serves as a valuable teaching tool when determining testing eligibility or demonstrating patterns of inheritance.

When collecting an individual's health history, there are several responses that may raise the concern for a potential

Table 1: Degrees of familial relations

First-degree relatives	Second-degree relatives	Third-degree relatives
Mother	Grandparents	First cousin
Father	Grandchildren	Great grandparent
Full sibling	Half-sibling	Great grandchild
Child	Aunt	Great aunt/uncle
	Uncle	
	Niece/nephew	
Shares 50% of the genes	Shares 25% of the genes	Shares 12.5% of the genes
Adapted from Roesser, 2010		

hereditary cancer syndrome as an explanation for the presence of breast cancer in the family pedigree. Special attention must be paid when a client states that there is a personal or family history of cancer before the age of 50, a personal or family history of more than one type of cancer or the same cancer occurring more than once, cancer in at least two generations in the family, the presence of male breast cancer, family history of certain types of cancer that fit a known hereditary pattern, and breast and/or ovarian cancer in an Eastern European Jewish family. The diagnosis of breast cancer in a family of Ashkenazi-Jewish ancestry may be suspect of a founder mutation seen in the BRCA genes. A founder effect exists when a mutation gene has a high frequency in a population of people who have a common ancestry and has periods when the population was isolated because of geographic proximity or culture.^[5]

Absolute cancer risk is the probability that an individual with given risk factors and a given age will develop cancer over a defined period of time.^[6] Developing statistical risk models that estimate the probability of developing cancer over a defined period of time will offer health-care providers the opportunity to identify those individuals with an increased risk for specific cancers. This identification facilitates the recommendation for earlier or more frequent screening and the provision of counseling on behavioral changes to decrease the risk. There are various models available to predict not only the risk of developing specific cancers, but also the risk of having a mutation in a gene that is associated with a specific hereditary cancer syndrome.^[5] It is vital for the health-care provider to take into consideration the strengths, weaknesses, and limitations of each model before selecting the most appropriate one.

The Breast Cancer Risk Assessment Tool (BCRAT) is based on a statistical model known as the "Gail model." The Gail model is the most widely utilized tool to identify the appropriate candidates for chemoprevention.^[7] This model takes into consideration a woman's personal medical history, reproductive history, and the history of breast cancer among her first-degree relatives. The model has been validated for Caucasian, Asian, and Pacific Islander women, but may underestimate the risk for breast cancer

in African-American women with previous breast biopsies. The Gail model needs further validation for Hispanic women and other subgroups as well.^[8] Several limitations in using the Gail model have been observed such as a limited use of maternal health history, no inclusion of paternal health history, and no consideration for the age of onset of breast cancer in the family. Clinicians will see on the website that the BCRAT is not intended to be used for risk calculation for those women who have: (1) had a prior diagnosis of breast cancer, ductal carcinoma *in situ*, or lobular carcinoma *in situ* (2) received previous radiation to the chest for treatment of Hodgkin's lymphoma, and (3) gene mutations in BRCA1 or BRCA2 or other genetic syndromes that may place them at an increased risk for breast cancer. As noted in the NCCN Guidelines, any woman with a 5-year risk of >1.7% determined by the Gail model can be considered for preventative therapy. The NCCN Breast Cancer Risk Reduction Panel has adopted the 1.7% or greater 5-year actuarial breast cancer risk defined by the modified Gail model as the risk threshold for discussion of chemoprevention. The Gail model can be accessed at www.cancer.gov/bcrisktool/.

The discussion of chemoprevention needs to address both the risks and benefits of the drugs being offered. Two selective estrogen receptor modulators that are frequently offered to high-risk women are tamoxifen (a drug used in the treatment of breast cancer) and raloxifene (a drug used to treat osteoporosis). Several randomized controlled trials have demonstrated that these two agents significantly reduce the incidence of invasive breast cancer in high-risk women. The Breast Cancer Prevention Trial revealed that tamoxifen reduced the risk of developing breast cancer by nearly one-half in both pre- and post-menopausal women; whereas, raloxifene was shown to have a similar benefit in the postmenopausal population.

Serious risk factors that need to be taken into consideration when counseling women on the use of tamoxifen include an increased risk for developing uterine cancer; venous thrombus events such as stroke, pulmonary embolus, and deep vein thrombosis; and an increased risk for the development of cataracts. Common side effects experienced when using tamoxifen include hot flashes and vaginal discharge. Raloxifene is not known to incur an increased risk for uterine cancer and has a lower risk profile for venous thromboembolic events. Common side effects of raloxifene include hot flashes, vaginal dryness, leg cramps, and weight gain.^[7]

The Tyrer-Cuzick model is a well-studied, widely available model for predicting breast cancer risk.^[9] This model includes the most complete set of data points and is the most sensitive of all the models for detecting the risk of

breast cancer. The model can be accessed at www.ems-trials.org/riskevaluator. (Please take note that version 8.0 is the most recent version of the risk assessment tool). The lifetime risk for developing breast cancer for an average-risk woman is 12%.^[7] The American Cancer Society, the NCCN, and the American Congress of Obstetricians and Gynecologists all recommend that, if a woman, aged 30 or older, has greater than a 20% lifetime risk for developing breast cancer, she should be offered an annual screening breast magnetic resonance imaging (MRI), in addition to an annual screening mammography. It is often suggested that these two imaging tests should be scheduled 6 months apart from one another. The main limitation noted when using the Tyrer-Cuzick model is that it only accounts for hereditary breast and ovarian cancers (HBOC).^[9] Mutations in the BRCA1 and BRCA2 genes are associated with HBOC. There are several other hereditary cancer syndromes that may increase the risk for developing breast cancer such as Li-Fraumeni syndrome (TP53 gene), Cowden syndrome (PTEN gene), Peutz-Jeghers syndrome (STK11 gene), and hereditary diffuse gastric cancer syndrome (CDH1 gene). Genetic counseling should be considered if a woman presents with any symptoms that may be of concern for the presence of any of these syndromes regardless of what the Tyrer-Cuzick score result is.

The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian^[10] states that genetic counseling is a critical component of the cancer risk assessment process. This type of counseling uses a broad approach to place genetic risk in the context of other related risk factors, fostering a personal approach based on the specific experiences of the individual. Genetic counseling provides the clients the ability to determine if they meet criteria for genetic testing as well as the opportunity to explore the risks and benefits of pursuing genetic testing. Counseling also creates a supportive environment to review the outcomes of cancer risk assessment and/or genetic testing and clarify how this information may influence the health management of the individuals and their family members. Individuals who are considering genetic testing need to be informed that test results may reveal a risk for cancers other than the cancer(s) initially motivated them to seek testing in the first place.

There are several hereditary cancer syndromes that have an increased risk for breast cancer. Table 2 displays three syndromes which have actionable recommendations and guidelines for those individuals who test positive for a pathogenic mutation in those genes. The recommendations for medical management are taken from the NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast and Ovarian, version 2.2017.^[10] These guidelines are

Table 2: Hereditary cancer syndromes associated with increased risk for breast cancer

Cancer syndrome	Associated gene	Associated cancers
Hereditary breast and ovarian	BRCA1 and BRCA2	Female and male breast, ovarian, fallopian tube, primary peritoneal, pancreatic, prostate, and melanoma
Cowden	PTEN	Endometrial, female and male breast, and follicular and papillary thyroid
Li-Fraumeni	TP53	Osteogenic and chondrosarcoma, rhabdomyosarcoma, breast, brain, leukemia, lymphoma, and adrenocortical carcinoma

Adapted from Roesler, 2010

periodically updated; please refer to the website at www.nccn.org for a complete listing of the most current version and recommendations.

There are several hereditary cancer syndromes with an associated increased risk for breast cancer. If a pathogenic mutation is found in any of those genes, it is important that the NCCN recommendations for medical management and screening guidelines should be discussed with both the clients and their medical providers to assure appropriate and consistent care.

Hereditary Breast and Ovarian Cancer

The overall prevalence of disease-related mutations in BRCA1/2 genes has been estimated as 1 in 300 for BRCA1 and 1 in 800 for BRCA2. Carriers of mutations in BRCA1/2 have an increased risk for both breast and ovarian cancers that warrants consideration of more intensive screening and preventative strategies.^[10] Women who test positive for a BRCA mutation should be counseled for the following medical management: engaging in breast self-awareness beginning at age 18, clinical breast examinations every 6–12 months beginning at age 25, annual breast MRI with contrast or mammogram if MRI is unavailable beginning at age 25–29, annual mammogram and breast MRI with contrast alternating every 6 months from ages 30–75, and after 75, medical management is based on an individual basis. Counseling with the woman should also include a discussion of risks and benefits of a risk-reducing mastectomy. The discussion of a risk-reducing salpingo-oophorectomy (RRSO) is generally offered to women between the ages of 35 and 40 and upon the completion of childbearing. Health-care providers may consider the option of a transvaginal ultrasound along with a serum CA-125 for those women who select to defer a RRSO.

Breast screening recommendations for men who are at high risk due to a pathogenic mutation in BRCA1/2 genes include education/training on breast self-awareness starting

at age 35 and clinical breast examination every 12 months beginning at age 35.

Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare heredity condition that is associated with a germline mutation in the TP53 gene. LFS is identified in approximately 1% of hereditary breast cancer cases. Screening recommendations for individuals affected with this gene mutation are similar to the HBOC guidelines. However, the age at which the screenings are offered may be younger due to the earlier onset of breast cancer. Women who are at high risk should be offered breast self-awareness beginning at age 18, clinical breast examination every 6–12 months beginning at ages 20–25, annual breast MRI screening with contrast is preferred or annual mammogram if an MRI is not available for women aged 20–29, annual mammogram and breast MRI screening with contrast for women aged 40–75, and after age 75, the management is decided on an individual basis. Mammography and breast MRI screening should be offered at the youngest age of diagnosis if there is a family history of breast cancer <20. Women who have been treated for breast cancer should have any remaining breast tissue screened with mammography and breast MRI. Due to the lack of data regarding risk-reducing surgery for women who are affected by LFS, counseling should be offered to address the risks and benefits on an individual basis.

Cowden Syndrome

The medical conditions that are a result of germline mutations in the PTEN gene are collectively known as PTEN hamartoma tumor syndrome. The conditions include Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, adult Lhermitte-Duclos disease, Proteus-like syndrome, and autism spectrum disorders with macrocephaly. Our discussion will focus on the screening recommendations for those individuals who are diagnosed with Cowden syndrome. The lifetime risk for breast cancer for women diagnosed with Cowden syndrome ranges from 25% to 50%, with an average age of 38–50 years at the time of diagnosis.^[10] There have only been two men affected by Cowden syndrome who have been diagnosed with breast cancer. Current medical management for breast cancer screening in an unaffected woman includes the following: annual physical examination beginning at age 18, women should begin regular monthly breast self-examinations at age 18 and should have clinical breast examination every 6 months beginning at age 25 or 5–10 years earlier than the earliest detected breast cancer in the family, and annual mammogram and breast MRI screening with contrast starting between the ages of 30 and 35 or 5–10 years

earlier than the earliest detected breast cancer in the family. Medical management for women over the age of 75 should be made on an individual basis. Women who have been diagnosed with Cowden syndrome and develop breast cancer should have an annual mammogram and breast MRI screening on any remaining breast tissue. Due to the lack of data regarding risk-reducing surgery for women who are affected by Cowden syndrome, counseling should be offered to address the risks and benefits on an individual basis.

Summary

The science of genetics (the study of heredity) and genomics (the study of genes and their functions) is the foundation of oncology nursing practice at the cellular level, as cancer is a complex disease consisting of multiple genetic changes.^[11] Regardless of their practice setting, oncology nurses have the opportunity to engage in the delivery of genetic and genomic services and the management of genetic information. All nurses at every level of academic preparation, role, or clinical specialty require genetic and genomic knowledge to identify, refer, support, and care for individuals affected by cancer.^[12] The International Society of Nurses in Genetics stated in their most recent edition of *Scope and Standards of Practice for Genetics/Genomics Nursing* as follows: “Genetics/genomics nursing is professional nursing care that focuses on the impact of genetic/genomic influences of health. Genetic/genomic nurses identify actual and potential genetic/genomic influences on health, educate clients and families on genetic/genomic influences that might impact their health, and intervene with the goals of optimizing health, reducing health risks, treating disease, and promoting wellness.”^[13]

The field of cancer genetic risk assessment will continue to expand as more nurses and health-care providers incorporate cancer risk assessment into their flow of patient care. It is important to remember that the research and evidence that supports the recommendations discussed in this article continues to evolve. It is recommended that those providers offering cancer genetic risk assessment should frequently review the data available on the NCCN website (www.nccn.org) to provide the most current and appropriate level of care to their clients.

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