REVIEW ARTICLE

Breast cancer in the young: role of the geneticist

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ABSTRACT

The genetics professional plays an important role in the care of young women with breast cancer by providing counseling on issues specific to these young women. The issues addressed in counseling include hereditary predisposition to cancer, fertility and reproductive options in the context of hereditary cancer, and the impact and implications of their history of early breast cancer on close family members.

A thorough risk assessment and counseling session address the patient's personal and family history, with particular attention paid to benign and malignant findings that suggest the need for genetic testing. Genetics professionals, especially genetic counselors, also address the physical and emotional implications of an increased risk of cancer with patients and family members. This review highlights the unique aspects of care provided by these specialized healthcare providers.

KEY WORDS Breast cancer; genetic counseling; risk assessment

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The role of the genetics professional in the care of young women with breast cancer is growing in recognition and importance. Genetics professionals are defined here as a geneticist, genetic counselor, or any health care provider specifically trained in clinical cancer genetics. This subset of health care providers offers patients a service that extends beyond the treatment of their breast cancer and guides management and screening to prevent the development of future cancers in the patient or her family members.

Approximately 1 in 200 women under the age of 40 were diagnosed with breast cancer in 2012 (1). In the context of breast cancer, "young women" is often defined as those under the age of 40. This population has unique considerations and challenges related to their cancer management. These include treatment-related infertility, pregnancy during or after treatment, and a higher likelihood of hereditary breast cancer compared to post-menopausal women (2,3). However, guidelines set forth by the National Comprehensive Cancer Network (NCCN) recommend further genetic risk evaluation among women age 50 or younger at the time of diagnosis (4). This genetic risk assessment includes an evaluation of personal and family history of several hereditary cancer syndromes. After obtaining a detailed personal and family history of breast cancer, the genetics professional counsels the patient about her potential health risks and provides reduction strategies for the patient and her family members. Here we review the genetic syndromes associated with breast cancer at a young age, describe the application of breast cancer risk models, and discuss recommendations and potential interventions for young breast cancer patients and their families.

Hereditary genetic syndromes associated with breast cancer

Given the complexity of hereditary breast cancer syndromes, young women with breast cancer may benefit from a formal risk assessment by a trained geneticist or genetic counselor. The risk assessment includes an evaluation of family and personal history to determine whether genetic testing is indicated. In the absence of an identifiable genetic cause for the family history of breast cancer, genetics professionals use the family history to guide management and to recommend breast cancer screening for patients and their family members (5).

This process involves gathering medical information from the patient for all family members, whether affected or unaffected. This information is then used to construct a detailed pedigree of three to four generations and includes first-degree relatives (i.e., parents, siblings, and children) and second-degree relatives (i.e., aunts, uncles, nieces, nephews, and grandparents). When collecting a cancer-focused medical and family history, the genetics professional identifies the type of cancer, age at

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diagnosis, number of primary tumors, primary *vs.* metastatic cancer sites, pathology, and prior treatment regimens (6,7). Other syndrome-specific details that may be included in the risk assessment include benign tumors, a history of non-cancer medical conditions, such as hypothyroidism, thyroid goiter, and fibrocystic breasts, and dermatologic findings, such as trichilemmomas, acrokeratosis, and fibrofolliculomas, among others (8). The genetics professional then uses this information to determine whether genetic testing is appropriate for the patient or for any of her family members. Based on pedigree analysis, the genetics professional estimates the likelihood of identifying a specific gene mutation by genetic testing (9). Using patient reports in genetic risk assessments has acknowledged limitations, such as inaccuracies in reported cancer histories, particularly in distant family members, as well as incomplete information, as is seen in small or adoptive families (10-13).

The majority of hereditary breast cancer is attributed to Hereditary Breast and Ovarian Cancer (HBOC) caused by mutations in *BRCA*1 and *BRCA*2 genes (14). *BRCA* mutations occur in approximately 1 in 400 to 1 in 800 individuals and are more common among those of Ashkenazi Jewish ancestry (1 in 40) (14-18). Among women with *BRCA* mutations, the lifetime risk of developing breast cancer is as much as 80%, and the increased risk of ovarian cancer in these women is as high as 45% (19,20). Increased risks of other malignancies, including male breast cancer, prostate cancer, and pancreatic cancer, also have been described in this population (21). Although the majority of hereditary breast cancer is associated with HBOC, a negative *BRCA*1 and *BRCA*2 test result may be uninformative in young women with breast cancer, because a negative result does not rule out the potential for a hereditary form of breast cancer in these patients (22).

Less common hereditary breast cancer syndromes also should be considered. Evaluation of personal and family history may prompt further investigation of more rare conditions. Li-Fraumeni syndrome, which is caused by mutations in the *TP53* gene, may account for 1% of all breast cancer (23). Mutations in the *TP53* gene also are associated with increased risks of several other types of cancer, including sarcomas (soft tissue and bone), brain, leukemia, and adrenocortical tumors (24). Although difficult to determine, the lifetime risk of cancer may be as high as 85% among individuals with *TP53* gene mutations (25,26). Often times the age of onset of these cancers, particularly breast cancer, are significantly younger than the ages of onset observed in the general population (23,24). Recent studies and an update to NCCN Guidelines suggest *TP53* genetic testing for women who are diagnosed at age 35 or younger and have negative *BRCA1* and *BRCA2* test results (27,28).

Further genetic evaluations of early-onset breast cancer may lead to testing for Cowden syndrome (associated with the *PTEN* gene), Peutz-Jeghers syndrome (*STK11* gene), or Hereditary Diffuse Gastric Cancer (*CDH1* gene) (29-31). Although these syndromes occur in fewer than 1 in 150,000 people, each syndrome is associated with an increased risk of breast cancer and other malignancies, some of which may have available screening for the patient and at-risk relatives.

Despite the identification of highly penetrant genes that are associated with hereditary breast cancer, a large proportion of breast cancer remains unexplained (32,33). Recent studies that have reviewed moderate- or low-penetrance breast cancer-susceptibility genes, such as *ATM*, *CHEK2*, *BRIP1*, *PALB2*, and RAD50, suggest that these genes account for some familial breast cancer cases (34,35). The risk of developing breast cancer among carriers of a low-penetrance gene is not well defined. As a result, standardized clinical management for these individuals and their family members is lacking and complicates the usefulness of ordering such testing (32,36).

Genetic risk assessment and genetic testing

The genetics risk evaluation of young women with breast cancer formally assesses the indication for genetic testing of one, or possibly several, hereditary cancer syndromes. The NCCN guidelines specify that women under age 45 are appropriate candidates for *BRCA* testing, with or without a family history of breast cancer. The guidelines also specify that women with breast cancer diagnosed under age 35 who have negative *BRCA*1/2 genetic test results should undergo *TP53* testing to rule out Li-Fraumeni syndrome (28). Although age of diagnosis may be an indication for genetic testing regardless of family history, the genetics professional will also review the woman's family history to ensure that the most appropriate genetic tests are ordered. The genetics professional must also ensure that all appropriate testing was performed and that reports of all previously performed genetic tests have been reviewed. Many young women who have had *BRCA* testing in the past may not have undergone large genomic rearrangement analysis because it was not clinically available at that time. In these situations, genetics professionals are likely to order additional testing to more completely rule out the possibility of hereditary cancer (37,38). Genetics professionals also may discuss DNA banking and or research opportunities with both the patient and her family members if a genetic explanation for the young woman's cancer cannot be found through currently available genetic testing (9). Patients are often encouraged to remain in contact with genetics professionals given that new genetic tests often become available, and newer tests may provide additional information to the patient and/or her family members (39).

During discussions of genetic testing, the genetics professional will review the risks, benefits, and limitations of testing, informed consent, and implications of test results. A review of the potential results of a genetic test includes positive,

true negative, uninformative negative, and variant of uncertain significance (VUS). A *positive* result indicates that a deleterious or pathogenic mutation has been identified in a cancer-causing gene, indicating an increased risk of cancer. A *true negative* result occurs when an individual undergoes site-specific genetic analysis for a known familial pathogenic mutation and is found not to be a carrier (8,9). An *uninformative negative* result describes the absence of an identified genetic mutation in the context of a personal or family history that remains concerning for a hereditary cause of cancer (8,9). An uninformative result also may be the consequence of testing an individual who was not the most appropriate family member to undergo testing. Genetic testing is most informative when performed on an individual whose personal history of cancer is most suggestive of the suspected hereditary cancer syndrome. This individual may be the one who was diagnosed with breast cancer at the youngest age in the family or the one most closely aligned with the concerning family history. Despite a diagnosis of early-onset breast cancer and possibly a family history of breast and ovarian cancer, many young women will not have a *BRCA* gene mutation (40). With an uninformative negative result, the genetics professional must re-evaluate the personal and family history in the context of this test result. For example, the genetics professional can consider whether the patient is a phenocopy, meaning a sporadic case of breast cancer in a family with hereditary breast cancer, or the family history may represent a familial clustering of cancer (41,42). Educating patients during the pre-test and post-test counseling is an important role of genetics professionals. The information enables patients to fully understand the implications and possible explanations for an uninformative negative genetic test result (43).

Providing an accurate interpretation and explanation of complicated test results is essential. This is particularly important when a VUS is found. A VUS is an alteration in the gene that may be either pathogenic or a benign polymorphism (8). Oftentimes, not enough data are available about the specific gene alternation to determine whether it is associated with an increased risk of cancer. As a result, when an individual is found to have a VUS, the clinical significance is not known and the medical management recommendations may not be clearly defined (8). Genetics professionals help patients understand the complexity of a VUS result and assist them in making decisions about medical care (44).

Risk assessment models

Several risk models have been developed to help determine the probability that a person will have a deleterious germline mutation that increases his or her risk of developing cancer. These are applied to support the genetic risk assessment achieved through pedigree analysis. These models also can estimate an individual's risk of developing breast cancer based on family history alone after common genetic syndromes have been ruled out. For example, models designed to calculate the likelihood of a *BRCA*1 or *BRCA*2 mutation include mutation prevalence tables reported by Myriad Genetic Laboratories, Inc.® in Salt Lake City, Utah, *BRCA*PRO, BOADICEA, and Penn II Risk Model, which are often used to estimate a probability range for the patient (45-49). Different models may be useful, depending on the available information for a particular family. *BRCA*PRO, for example, is a commonly used mathematical model that utilizes Bayesian analysis to calculate the probability of a *BRCA* gene mutation for the patient based on the family history of breast and ovarian cancer in first- and second-degree relatives (46). The BOADICEA model was developed in the United Kingdom by using population-based studies that evaluated patients with breast and ovarian cancer. This model integrates the possibility of genetic modifiers and accounts for other *BRCA* -associated cancers (i.e., prostate, pancreatic, and male breast cancer) in the risk assessment (41,47,48,50). Each model has a unique set of strengths and limitations that can support the clinical judgment of the genetics professional (51). Not every hereditary cancer syndrome has available risk models; therefore, primary literature also may be used to assist in the risk assessment. For example, a scoring system and an online tool can be used to estimate the risk of a *PTEN* mutation based on the presence or absence of associated Cowden syndrome features (52).

Other empiric risk models also are available to estimate the lifetime risk of developing breast cancer among unaffected women with particular personal and family history risk factors. Among these risk estimation models are the Gail model, which is available through the National Cancer Institute, Claus model, and Tyrer-Cuzick models (5,53,54). These tools are designed to help guide management recommendations for unaffected family members of young breast cancer patients; however, each model is dependent upon different sets of criteria. The Gail model may identify a woman at increased risk of breast cancer according to personal risk factors, such as current age and history of breast biopsies, and may guide recommendations for tamoxifen use. In contrast, the Claus model takes into consideration the breast cancer history of first- and second-degree relatives, and the results of the risk estimate may lead to a recommendation of increased breast cancer screening, such as breast MRI (55,56). The younger the age at breast cancer diagnosis among first- and second-degree relatives, the greater the likelihood that an individual will be advised to receive increased breast surveillance (5). The Tyrer-Cuzick model uses both personal risk factors and family history to calculate the likelihood of a *BRCA* mutation as well as the lifetime risk of developing breast cancer in the absence of a *BRCA* mutation. This statistical model also incorporates the chance of a low penetrance gene mutation, unlike the other models available for unaffected women (54).

Potential recommendations and interventions

Identifying women with a hereditary cancer can alter treatment plans, surgical options, and/or future screening and management. Genetics professionals make management recommendations for the entire family based on genetic test results and/or cancer risk assessment models (8). Young women who test positive for a specific gene mutation (i.e., *BRCA*1/2, *TP53*, *PTEN*) are informed about management options specific to the associated hereditary cancer syndrome. Sources of consensus for management guidelines in the U.S. include organizations such as the NCCN and the American Cancer Society (8). Unfortunately, specific management guidelines are not available for many hereditary cancer syndromes, often because of their rarity and the lack of screening modalities. Recommendations are often extrapolated from the guidelines for HBOC; however, the efficacy of these recommended interventions will vary by syndrome and/or by family because of the variation in cancer risks (8).

Although a small subset of young women with breast cancer will be found to have a hereditary cancer syndrome, the majority will receive negative results from their genetic testing. For families with an uninformative negative test result, genetics professionals base screening and management recommendations on empiric risk data that account for the family history, often using such models as Claus or Tyrer-Cuzick (8). Screening recommendations for unaffected close female relatives of the young patient may include regular breast self-exams, clinical breast exams, earlier mammography, and/or increased screening that includes breast MRI, as these are the management recommendations for women at an increased risk for hereditary breast cancer (57). The age of initiation of screening is often based on the earliest age of diagnosis in the family (i.e., begin mammography 10 years earlier than the youngest age of breast cancer diagnosis in the family) (58,59).

Management of young women with hereditary or familial breast cancer also may entail several potential interventions. These include enhanced breast screening, surgical prevention strategies, and chemoprevention (57). Women with a diagnosis of a hereditary cancer syndrome may also be at an increased risk for several other types of malignancies. These include, but are not limited to, ovarian cancer, endometrial cancer, colon cancer, thyroid cancer, melanoma, and pancreatic cancer. Depending upon the clinical genetic syndrome, patients may require more individualized screening recommendations (60). These recommendations are often guided by consensus guidelines (such as those from NCCN) or, in the absence of consensus guidelines, clinical judgment and pertinent research from the medical literature. The recommendations may include annual dermatological evaluations, colonoscopy, thyroid cancer screening, or other appropriate tests (4,8).

Beyond the immediate management of young women with breast cancer, there are additional considerations regarding fertility preservation and future pregnancies. The American Society of Clinical Oncology states that early in treatment planning these young women should be engaged in a discussion of their options for fertility preservation (61). As part of a multidisciplinary team, genetics professionals may be one of the first points of contact in a young woman's treatment plan, and referral to a reproductive endocrinologist may be expedited (62). A genetics consultation regarding a young woman's potential hereditary cancer syndrome may also address fertility preservation, possible genetic risks for future offspring, and reproductive options, such as pre-implantation genetic diagnosis (PGD) (63). PGD is one form of early prenatal diagnosis that is performed on embryos obtained through *in vitro* fertilization. An embryo can be tested for a specific genetic condition. If the embryo is found to have the gene profile for the condition in question, an unaffected embryo can be chosen for implantation (64,65).

Inadequate knowledge of PGD is common among individuals at high risk for hereditary cancer and among healthcare providers (66,67). Julian-Reynier and colleagues surveyed nearly 400 unaffected *BRCA*-positive carriers and found that 85% of respondents expected information about prenatal diagnosis. The women also expected to have PGD information provided by a cancer geneticist at the time the genetic test results were reported (68). This clearly highlights the need for patient education, but no standard clinical practice or professional guidelines are available for consumer education about PGD (69).

The implications of hereditary breast cancer among young women are complex and require attention from many different, specialized providers. Genetics professionals are responsible for educating these patients about the clinical implications of their conditions (8). Oftentimes, the genetics professional will refer patients to the appropriate healthcare providers so that screening and/or preventative surgery specific to that particular genetic syndrome can be discussed (8).

The identification of a hereditary cancer syndrome in a family has implications not only for the physical health of the individuals involved, but also for their emotional health and well being. Genetics professionals, especially genetic counselors, are responsible for addressing the possible medical and psychological implications of genetic test results (8). Genetic counselors address psychological issues such as worry about cancer, anxiety, intrusive thoughts, depression, anger, fear, guilt, family experiences with cancer, risk perception, social stressors, support and family networks, family communication, and readiness for genetic testing (8). Pre-test psychosocial assessment prior to genetic testing has been recommended to gauge a patient's anxiety level, as studies have shown that high pre-test anxiety is associated with higher post-test anxiety (70). The genetic

counselor often assesses the psychosocial needs of the patient and provides assistance in managing the psychosocial responses that often occur in families that have an increased risk of developing cancer (71). Providing emotional support, reducing isolation, bolstering existing support networks, and designing innovative support interventions (i.e., multi-family support networks) have been suggested as methods for addressing the psychosocial needs of young patients with hereditary breast cancer (72). It has been suggested that formal support services for this patient population are unavailable or underutilized (72). If such support is available, genetic counselors educate patients about support groups and other resources, including peer support, Internet-based support organizations, and patient-focused gatherings on hereditary cancer (73,74). Web-based support groups also have been shown to be effective in reducing psychological distress (75). Some individuals, particularly young women, may require additional long-term support services. In these situations, genetics professionals often refer patients to long-term psychotherapy, marriage and family therapists, social workers, sexual rehabilitation counselors, depending upon the patient's needs (72). Unique psychosocial considerations for young women with hereditary breast cancer include an urgency to find a life partner and begin a family. This urgency arises from the possibility of surgical implications, the impact of genetic test results on relationship building (family and social relationships), risks to future offspring, sexuality challenges, limited availability of peers in similar circumstances, impact on career building, and other concerns related to their situation (76-78). Because of these unique and complex challenges, young women may be more likely to require long-term support and referrals to psychotherapy services.

Another unique role of genetics professionals is identifying at risk-relatives and facilitating family communication regarding genetic test results and increased cancer risks. Genetics professionals first analyze the family history (pedigree) and discuss the most likely origin of inheritance in the family (i.e., maternal, paternal, or de novo). If the origin of the mutation is unclear based on the family history, the genetics professional will identify relatives who should be tested to determine which lineage is at-risk for the particular hereditary cancer syndrome.

Genetics professionals have a duty to inform their patients about the implications of their test results for their family members, while also protecting the patient's confidentiality (79,80). Patients with a positive test result are urged to notify at-risk relatives who may benefit from genetic testing (8). Genetics professionals also inform patients that negative genetic test results (uninformative negative or true negative) may still impact relatives' decision-making regarding genetic testing and/or medical management (81). Family members of patients with negative genetic test results need to be informed about the potential for an increased risk of breast cancer. As previously mentioned, risk models, such as the Claus model, can be used to determine whether close female relatives (i.e., daughters, sisters, mothers) may need to be followed with increased breast cancer screening (5).

Communication of information regarding hereditary cancer and the potential increased cancer risks to family members may be an emotionally overwhelming process for patients (82). Genetics professionals, particularly genetic counselors, play an important role in facilitating the communication process between the patient and his or her at-risk relatives (71). Follow-up genetic consultations after the disclosure of test results increase the proportion of relatives who are informed of their genetic risk (83).

This follow-up support often includes resources and written materials that can be shared with family members, such as individualized summary letters for the family and educational materials (81). Both male and female relatives need to be informed; however, patients are more likely to disclose their genetic results to female relatives than to male relatives (84). This may be attributable to the focus on the increased risk for breast cancer in females. Genetics professionals are responsible for educating their patients about cancer risks for males that are associated with the various hereditary cancer syndromes and for encouraging patients to inform both male and female relatives (81).

In addition, young breast cancer patients often have young children; therefore, the disclosure of genetic test results to children is another challenge that is addressed. The age at which test results are disclosed to children is often dependent on the hereditary cancer syndrome. For example, parents may wish to disclose their results and test their children for a *TP53* mutation, which confers an increased risk of certain childhood cancers. In contrast, individuals with a *BRCA* mutation may choose to delay disclosure until children are older, given that testing is not typically recommended for minors because the results lack clinical significance for children. Genetics professionals, most often genetic counselors, raise the issue of communication of genetic test results between parents and offspring and provide anticipatory guidance regarding the potential implications of sharing or not sharing the information with their children (85).

Conclusions

Genetics professionals play an important role in helping young women with breast cancer, who have a higher likelihood of having an underlying hereditary cancer syndrome. To provide the best care for these women, genetics professionals should offer a cancer genetics risk assessment that will provide a thorough evaluation of personal and family history features that may indicate the need for genetic testing. Education and counseling are essential for these young women, who need to understand

the possible implications of test results for them personally and for their family members.

Genetics professionals can offer recommendations to guide cancer screening and management based on the outcome of genetic tests. The goal is to prevent future malignancies and to ensure that any malignancies that do develop are diagnosed early. The role of the genetics professional is unique in that it extends beyond the current cancer diagnosis and focuses on the future health and well-being of the young women and their family members.

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