Hereditary Breast and Ovarian Cancer Syndrome

NICOLETTA CAMPAGNA, RN, MSN, DNP, APRN-BC, AOCNP®

From Cancer Treatment Centers of America, Western Regional Medical Center®, Zion, Illinois

Author's disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Nicoletta Campagna, RN, MSN, DNP, APRN-BC, AOCNP®, 4715 83rd Place, Kenosha, WI 53142.
E-mail: campagnana@yahoo.com

J Adv Pract Oncol
2011;2:257–262

With the discovery of *BRCA1* and *BRCA2*, a new area of cancer genetics emerged. As knowledge of cancer genetics has increased, so has awareness of cancer genetics among health-care providers and the general public. Advanced practitioners can be instrumental in identifying patients, informing patients, families, and the public about the implications of these findings in terms of cancer prevention, early detection, and treatment. It is essential to determine appropriate candidates for genetic testing and discuss the risk-to-benefit ratio of testing with them. Taking a thorough and accurate history from both sides of the family is the first step in this process, as half of all *BRCA1* or *BRCA2* mutations are inherited from the paternal side of the family (Roesser, 2003).

Hereditary breast and ovarian cancer (HBOC) syndrome is an inherited condition that makes one's risk of developing breast and/or ovarian cancer higher than average. Families with HBOC syndrome typically have two or more family members who develop breast or ovarian cancer, often before age 50, and may not have other warning signals or "red flags" that suggest the possible presence of HBOC (see Table 1).

The National Comprehensive Cancer Network (NCCN) strongly encourages the involvement of a genetic counselor and/or a medical geneticist early on in counseling patients who may meet criteria for any inherited syndrome (NCCN, 2010). Genetic counseling is strongly recommended at the time testing is offered and after results are disclosed as well.

About 5% to 10% of all cancers are caused by abnormal changes in the genetic code passed down from a parent in the form of an inherited gene mutation. HBOC syndrome is caused by mutations on the *BRCA1* or *BRCA2* gene. There is a 50% chance that the *BRCA1* and/or *BRCA2* mutation will pass from a parent who carries the mutation to each child (Tranin, Masny, & Jenkins, 2006). This greatly increases the risk of developing breast or ovarian cancer (see Figure 1).

Cancer risks associated with mutations in *BRCA1* and *BRCA2* include a lifetime risk of female breast cancer approaching up to 85% by age 80, with much of that risk occurring by age 50, when traditional screening tools such as mammograms are the least sensitive (Barcenas et al., 2006). Women who carry the mutations also face higher risks for ovarian cancer, a disease in which screening and early detection remains elusive. Lifetime ovarian cancer risks vary by gene; women with the *BRCA2* mutation have a 10% to 20% risk, and women with the *BRCA1* mutation have about a 20% to 40% risk (Barcenas et al., 2006).

Case Study

A.G. is a 56-year-old Caucasian female with metastatic breast cancer who was originally diagnosed with breast cancer at age 41, in 1995, when she presented to her primary care physician with a right breast mass. This was the same year that *BRCA1* and *BRCA2* mutations were being discovered. A biopsy was done, revealing her mass to be a 2.8-cm infiltrating ductal carcinoma that was grade 3 ER/PR positive. She was staged as T2NxMx. She underwent a right modified radical mastectomy with reconstruction with a transverse rectus abdominis myocutaneous (TRAM) flap. Pathology revealed 0 out of 13 nodes to be positive.

A.G. received adjuvant therapy with 4 cycles of doxorubicin/cyclophosphamide followed by 5 years of tamoxifen. There was no evidence of disease for 13 years, until 2008, when A.G. developed right upper arm swelling; venous Doppler revealed an occlusive thrombus in the right axillary vein. A chest CT scan showed osseous metastatic disease involving the sternum and anterior right first rib with an extraosseous soft-tissue mass. There was also a small right pleural effusion, suspicious mediastinal lymph nodes, and multiple pulmonary nodules.

A bone scan confirmed multiple skeletal metastases involving the left posterior skull, right first rib, sternum, left posterior iliac bone, and left femoral head. One of the nodules was biopsied, revealing metastatic carcinoma compatible with breast primary. A.G. was started on zoledronic acid (Zometa) and letrozole in April 2008. In July 2008, a CT scan of the chest showed interval resolution of the thoracic adenopathy, near resolution of the bilateral pulmonary nodules, and mixed lytic and blastic lesions involving the bones. Fulvestrant (Faslodex) was then added to the treatment plan. In January 2009, A.G. was switched to tamoxifen and fulvestrant was discontinued.

In June 2009, PET scan revealed an increase in the size of the parasternal mass along with increased density in the mediastinum. Estradiol was added outside of a clinical trial. Follow-up PET/CT in September 2009 showed significant progression, and A.G. was switched to exemestane. She had spent a total of 4 months on estradiol. One may question the use of estradiol in hormone receptor–positive breast cancer. This was actually examined as practice between 2004 and 2008 in an effort to resensitize to estrogen deprivation in postmenopausal women in aromatase inhibitor–resistant breast cancer (National Cancer Institute, 2010). In this case, the problem is that A.G. was not given any aromatase inhibitors at this point; this practice could very well have contributed to the progression of her disease.

By November 2009, A.G.'s CEA and CA 15-3 levels started to rise, and she was found to have right supraclavicular, axillary, subclavian, mediastinal, parasternal, and pleural-based metastatic disease. Exemestane was stopped and A.G. was started on capecitabine (Xeloda). In February 2010, she received radiation to the T10 and L1 vertebrae for her bone metastases.

In March 2010, PET/CT revealed innumerable hypermetabolic soft-tissue masses in the lymph nodes, lung nodules, and bones. Five radiation treatments were delivered to the sternum and right chest wall in July 2010. By the end of July, A.G. developed a large pleural effusion and underwent an ultrasound-guided thoracentesis, withdrawing 1.5 L of pleural fluid that was positive for metastatic adenocarcinoma. Capecitabine was stopped at this time due to progression, and she was told by her oncologist that nothing more could be done.

A.G. self-referred to another oncologist in July 2010. Family history revealed that her mother had been diagnosed with breast cancer at age 48, and that her two sisters were diagnosed with breast cancer at ages 45 and 47 and found to be *BRCA2*-positive with deleterious mutations noted at 6855ins TA. One sister had the full BRAC*Analysis* in February 2010 and the other sister was tested for specific mutation in April 2010. Although their mother was the first to be diagnosed with breast cancer, it was more than 20 years ago; she did not choose to have any type of genetic testing done. A.G. reported that she had been tested with the full *BRCA* panel in February 2009 and had been found to be negative. (See the accompanying text for more information about A.G.'s case.)

Table 1. Further Risk Evaluation Criteria for HBOC Syndrome

One or more of the following[a]:

- Early-onset breast cancer age 50 or younger
- Two breast primaries (including bilateral disease) *or* instances where there are two or more clearly separate ipsilateral primary tumors *or* breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual or close relative(s) from the same side of family
- A combination of breast cancer with one or more of the following: thyroid cancer, adrenocortical carcinoma, sarcoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer (with lobular cancer), or leukemia/lymphoma on the same side of the family
- Member of a family with known mutation in a breast cancer susceptibility gene
- Male breast cancer
- Ovarian/fallopian tube/primary peritoneal

Note. HBOC = hereditary breast and ovarian cancer. Based on information from National Cancer Institute (2009) and National Comprehensive Cancer Network (2010).
[a]Populations at risk, such as those of Ashkenazi Jewish descent, would have lessening of inclusion criteria, i.e., breast or ovarian cancer occurring at any age.

Genomics in Oncology

As evidence continues to show that most diseases and conditions have a disruption in the genetic component, genomics has been receiving more and more attention (Mahon, 2009). Genomics differs from genetics in that genetics scrutinizes the function and composition of the single gene, whereas genomics deals with all genes and their interrelationships to identify their combined influence on the growth and development of the organism as a whole (World Health Organization, 2002). Advanced practitioners (APs) must understand genomics and the role it plays in oncology. Oncology is one of the first subspecialties to feel the full impact of the genomics revolution in prevention, screening, diagnosis, prognosis, selection of treatment, and monitoring of treatment effectiveness.

One of the single most important things that an AP should be able to accomplish is eliciting, verifying, and constructing a minimum three-generation family history, or pedigree, using standard nomenclature (Mahon, 2009). See Figure 2 for an explanation of the symbols used in this standard system.

Based on available information and employing standard nomenclature, A.G.'s pedigree would look like the one shown in Figure 3.

Case Study Follow-Up

Based on a family history with three first-degree relatives having early-onset breast cancer, two sisters having the mutation, and early-onset personal cancer, A.G. was retested for the specific deleterious mutation noted at 6855ins TA that was found in her sisters; she was found to be positive for the mutation. She was referred for genetic counseling. It was strongly recommended that A.G.'s adult son and daughter be made aware of the specific gene mutation that their mother has, and that they receive genetic counseling as well.

Because A.G. already had metastatic disease, removal of the opposite breast was not recommended; however, prophylactic oophorectomy was. She underwent bilateral oophorectomy, and is currently being followed by a genetic counselor. The soft-tissue masses, pleural effusions, and lymphadenopathy have resolved, and A.G. is currently being treated for bone-dominant breast disease, with an Eastern Cooperative Oncology Group performance status of 0.

Another potential test for A.G. would have been the BRAC*Analysis* Large Rearrangement Test (BART) (Myriad Genetics Laboratory, 2010). Because large genomic rearrangements occur in a small percentage (< 1%) of all patients tested for HBOC syndrome, BART was launched in 2006 as an enhancement to the comprehensive BRAC*Analysis* test that detects five common large rearrangements in both the *BRCA1* and *BRCA2* genes.

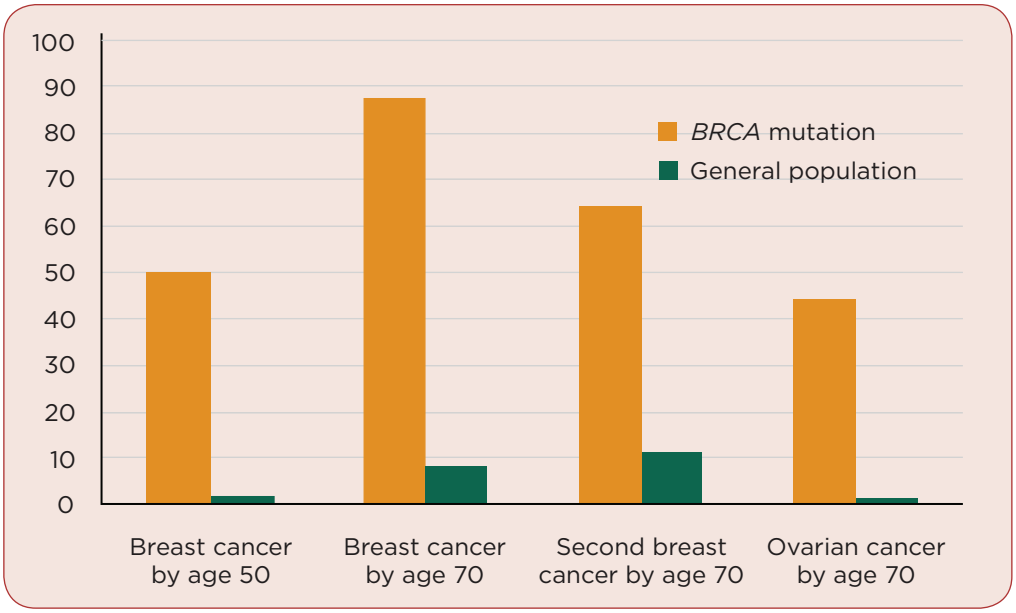

Figure 1. Risk of developing cancer with or without HBOC syndrome. Based on information from Tranin, Masny, & Jenkins (2006).

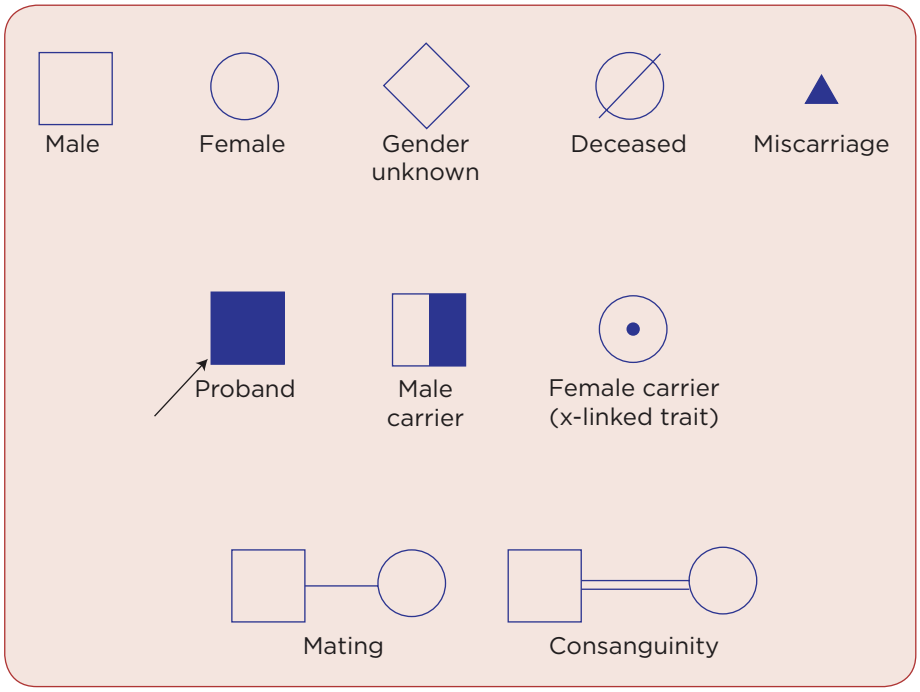

Figure 2. Standard pedigree nomenclature. Based on information from Jorde, Carey, & Bamshad (2010).

APs and Genetic Counseling

Advanced practitioners are the ideal clinicians to expand their skills and become actively involved in the role of genetic counseling. The Genetic Nursing Credentialing Commission (2011) has outlined a very specific credentialing process for those interested in earning the Advanced Practice Nurse in Genetics credential, which focuses on clinical experience, academic courses, and portfolio acquisition (Mahon, 2009). At present, there are only 0

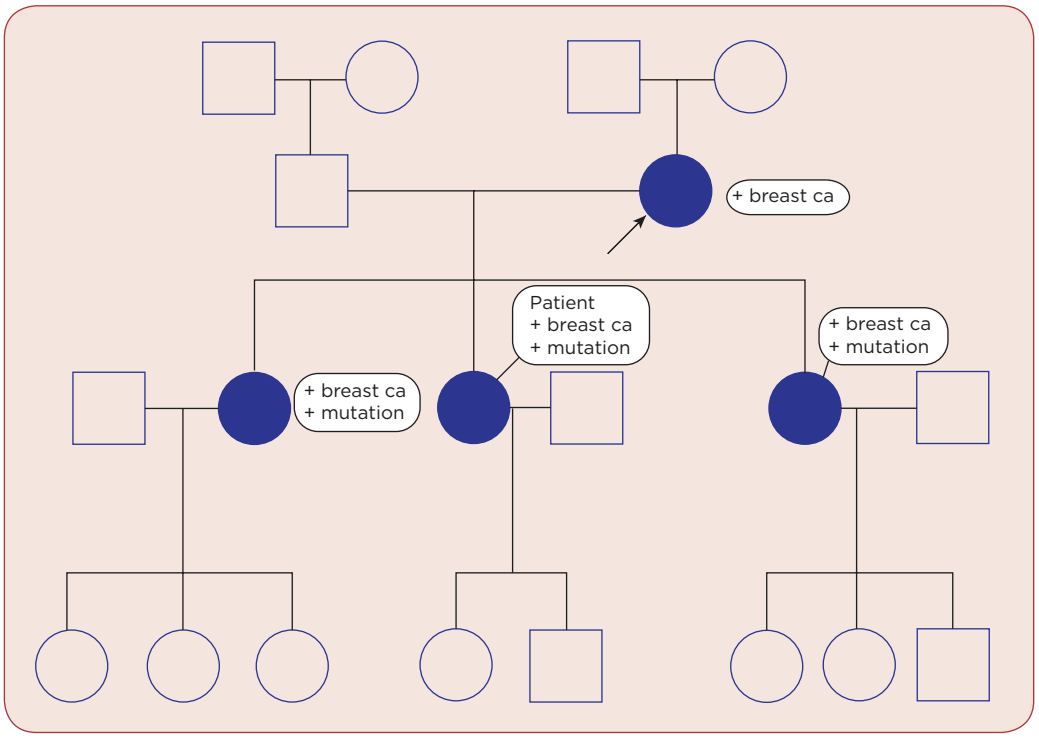

Figure 3. A.G.'s pedigree

to 4 people per state who have this credential. This limited number of available clinicians makes it difficult at times to get patients and families into the process before the testing is even done, as is recommended in the NCCN Practice Guidelines for Breast and/or Ovarian Cancer Genetics (NCCN, 2010).

Conclusions

Managing cancer risk for women with the *BRCA1* or *BRCA2* mutation is very complex. It includes options for risk-reducing surgery, intensified cancer screening and surveillance, chemoprevention, and risk avoidance. Managing HBOC risk in young women presents special challenges for health-care providers. Knowledge and practices based on average risk are not completely applicable to young women with HBOC risk. Despite intense accumulation and examination of evidence regarding the efficacy of each strategy, the management of HBOC risk is complicated by the life-planning issues typically faced by young, single women (Berliner & Fay, 2007). For example, uncertainty about whether or when cancer might strike changes the timing of risk management into a gamble against the odds that putting off surgery until childbearing is complete will be safe.

It is necessary for APs to keep up with current recommendations and information, know how to recognize high-risk family histories, and have a different index for suspicion of symptoms (Khoury-Collado & Bombard, 2004). Unfortunately, studies have shown that provider knowledge can fall short, such as failing to realize that *BRCA* mutations can be paternally transmitted (Khoury-Collado & Bombard, 2004). Advanced practitioners should be sensitive to how risk management recommendations will be perceived by the patient. We, as APs, must be prepared to offer support and referrals as patients process—both intellectually and emotionally—how they will incorporate their risk information into their lives.

Use your smartphone to view the GNCC's requirements for the Advanced Practice Nurse in Genetics credential.

SEE PAGE 268

DISCLOSURE

The author has no conflicts of interest to disclose.

REFERENCES

Barcenas, C. H., Hosalin, G. M., Arun, B., Zong, J., Zhou, X., Chen, J., & Amos, C. I. (2006). Assessing BRCA carrier probabilities in extended families. *Journal of Clinical Oncology, 24*, 354–360. doi:10.1200/JCO.2005.02.2368

Berliner, J. L., & Fay, A. M. (2007). Risk assessment and genetic counseling for hereditary breast and ovarian cancer: Recommendations of the National Society of Genetic Counselors. *Journal of Genetic Counseling, 16*, 241–260. doi:10.1007/s10897-007-9090-7

Genetic Nursing Credentialing Commission (2011). Advanced practice nurse in genetics. Retrieved from http://www.geneticnurse.org/advancedpracticeapng.html

Jorde, L. B., Carey, J. C., & Bamshad, M. J. (2010). *Medical genetics* (4th ed.). Philadelphia: Mosby.

Khoury-Collado, F., & Bombard, A. T. (2004). Hereditary breast and ovarian cancer: What the primary care physician should know. *Obstetrical and Gynecological Survey, 59*, 537–542.

Mahon, S. M. (2009). Cancer genomics: Advocating for competent care for families. *Clinical Journal of Oncology Nursing, 13*(4), 373–376. doi:10.1188/09.CJON.373-376

Myriad Genetics Laboratory (2010). Myriad for professionals. Retrieved from http://www.myriadpro.com/BRAC_BART

National Comprehensive Cancer Network. (2010). NCCN practice guideines: Breast and/or ovarian genetic assessment. Retrieved from http://www.nccn.org

National Cancer Institute. (2009). NCI fact sheet: BRCA1 & BRCA2 cancer risk and genetic testing. Retrieved from http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA

National Cancer Institute. (2010). Clinical trial identifier NCT00324259. Retrieved from http://www.cancer.gov

Roesser, K. A. (2003). Understanding hereditary breast and ovarian cancer. *Clinical Journal of Oncology Nursing, 7*(5), 591–594. doi:10.1188/03.CJON.591-594

Tranin, A. S., Masny, A., & Jenkins, J. (eds.). (2006). *Genetics in oncology practice: Cancer risk assessment* (2nd ed.). Pittsburgh: Oncology Nursing Society.

World Health Organization. (2002). Genomics and world health: Report of the Advisory Committee on Health Research. Retrieved from http://whqlibdoc.who.int/hq/2002/a74580.pdf