

Understanding the Genetics of Breast Cancer: A Clinical Overview

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Abstract

Breast cancer is the second leading cause of death among women in the United States, exceeded only by lung cancer.¹ An estimated 5 to 10% of all breast cancers are inherited, and the breast cancer susceptibility genes BRCA1 and BRCA2 have been identified as being responsible for 21 to 40% of these cases. Furthermore, women who carry a germline mutation in BRCA1 have a cumulative lifetime risk for developing breast cancer of 50 to 85%.² Comprehensive genetic counseling that includes risk assessment, genetic testing, surveillance, and preventative strategies are essential for women who have been identified as being at high risk for inherited breast cancer. Accordingly, this paper will review the genetic component of breast cancer and the recommendations for screening and clinical management in this population of patients.

INTRODUCTION

Much attention has been focused on breast cancer and its treatment, yet many argue that the most effective means of reducing breast cancer is through preventative breast cancer interventions that focus on indentifying high risk individuals who are most likely to benefit from aggressive risk reduction measures.³ For women in the United States, breast cancer is the second leading cause of cancer deaths, exceeded only by lung cancer.¹ Breast cancer must be diagnosed at the earliest possible stage in order to provide the most favorable chance of survival. Women with an increased risk are those with a family history of breast cancer, especially if the cancer occurs in a first degree relative such as a mother, sister, or daughter.⁴ If more than one first degree relative has developed breast cancer, especially below the age of 40, the cancer is likely that the cancer is due to an inherited mutation in the breast cancer susceptibility genes BRCA1 or BRCA2.³ This paper will review the genetic component of the BRCA1 and BRCA2 genetic mutations and the screening and clinical management recommendations for this population of patients.

GENETIC DISEASE OVERVIEW

In considering the genetic causes of breast cancer, BRCA1 and BRCA2 mutations are the most commonly occurring genetic mutations found. In 2007, approximately 178,480 new cases of invasive breast cancer were diagnosed among women, and of those women diagnosed, 40,460 women will

die of this disease. Additionally 10% of breast cancers can be linked directly to germline mutations in BRCA1 and BRCA2.¹ The prevalence of heterozygous carriers of high-risk mutations in the general population is estimated to be around one in 1000 for BRCA1 and one in 750 for BRCA2.⁵

The BRCA1 gene was localized to chromosome 17q21 by linkage analysis in 1990. From that time until 1992, research in this area expanded and the chromosome 17q location was confirmed by demonstrating loss of heterozyosity in breast and ovarian cancer samples.⁶ In 1994 the BRCA1 gene was cloned and the BRCA2 locus on chromosome 13q12.3 was identified. The following year, research findings indicated that some sporadic ovarian cancers had mutations from the BRCA 1 gene. In that same year, the BRCA2 gene was isolated. Research in the area continued to evolve, and in 2002 microarrays demonstrated how breast cancer patients could be stratified to high and low risk groups.⁶

The BRCA genes are considered caretaker genes. These genes act as sensors for DNA damage and participate in the repair process. The inactivation of these genes allows for other genetic defects and leads to genetic instability.⁷ For both BRCA1 and BRCA2 genes, the cancer risks are influenced by the position of the mutation within the gene sequence.⁶ The BRCA 1 gene is located on chromosome 17q21, whereas the BRCA2 gene is located on chromosome 13q12. BRCA 1 has 22 exons and spans approximately 100 kb of genomic DNA and encodes 1863 amino acid proteins.

BRCA 2 has 27 exons and spans approximately 70 kb and encodes a protein of 3418 amino acids. ⁶ Women with a mutation in the central region of the BRCA1 gene have been shown to have a lower risk than women with mutations outside the central region. For BRCA2 mutations in the central region, there is a higher risk of ovarian cancer and a lower risk of breast cancer than mutations outside this region. ³⁶

Mutations in the BRCA genes are transmitted through the germline in an autosomal dominant pattern of Mendelian inheritance. A person with a germline BRCA gene mutation possesses one mutated allele and one normal allele. The second normal allele is deleted, which leads to a complete loss of function. ⁶⁸ A child born to a parent with a BRCA mutation has a 50% chance of inheriting the mutated gene, and not all carriers of a BRCA mutation will develop cancer. Males with BRCA mutations may not develop the disease, thus paternal inheritance may result in skipped generations. ²⁶

Other genes, such as the TP53 have been implicated in familial breast cancer. This gene is associated with Li-Fraumeni Syndrome. The TP53 gene is located on chromosome 17p13 and is a tumor suppressor gene. ⁶ The cellular alteration that occurs as a result of this mutation is responsible for causing cancers such as leukemia, brain cancer, osteosarcoma, and breast cancer. ⁶ The inherited mutation in the PTEN gene is associated with Cowden Syndrome and, although uncommon, has also been reported as a genetic cause of breast cancer. Women carrying the PTEN mutation have a 25 to 50% lifetime breast cancer risk. ⁷ Women with Cowden Syndrome are also at risk for thyroid and endometrial cancers. ⁶⁷

ASSESSMENT FOR HEREDITARY BREAST CANCER

The characteristics of inherited breast cancer include breast cancer diagnosed prior to the age of 40; multiple cases of breast or ovarian cancer in the same patient or close blood relative; a family member with a known mutation in a breast cancer susceptibility gene; a family history of male breast cancer, or a clustering of breast cancer with other cancers related to Li-Fraumeni syndrome or Cowden syndrome. ⁹ Hereditary breast cancers are also clustered among certain ethnic groups such as African American and Asian women. In the Ashkenazi Jewish population, three particular alterations have been found, two in the BRCA1 gene and one in the BRCA2 gene. ¹⁰

An accurate family history is the key to identifying a patient with a genetic predisposition to breast cancer. ⁹ The family history should begin with the index case or family member through whom a genetic disorder is associated. Once the index case has been identified, the history should proceed outward to include first, second and third degree relatives on both the maternal and paternal sides. ⁹ The information collected should include cancers diagnosed by primary site, age at diagnosis, bilaterally occurring breast cancers, and current age or age at death. Other medical conditions, such as Cowden syndrome that may predispose a person to breast cancer, must also be collected as part of the family history. ⁹

GENETIC COUNSELING AND TESTING

Woman identified as meeting the criteria for hereditary breast cancer should be offered genetic counseling. Genetic counseling and evaluation offers women the support and information needed to make informed decisions about genetic testing. Referral to a genetic counselor is essential to ensure the linkage of testing with appropriate management decisions. ¹¹ Genetic counseling assists in discussing the ethical, legal, and social consequences of genetic testing. Among the issues that may be addressed by the genetic counselor are the potential for burdening patients with the knowledge of mutations of unknown importance and the potential for affecting family members other than the patient. ¹²¹³

When identifying patients to refer for genetic counseling and testing, health care providers must be aware of certain cultural and ethnic implications. Olopade, Fackenthal, Dunston, Tainsky, Collins, and Whitfield-Broome reported that Caucasian women from socioeconomically advantaged circumstances comprise the majority of clients who use genetic counseling and testing options. Therefore, minorities are less likely to use cancer genetic counseling services unless a major outreach effort is directed toward inclusion of minorities. ⁵

The decision to proceed with genetic testing must be an informed decision based on counseling regarding the risk-benefit ratio and the cost of the test; therefore the importance of genetic counseling cannot be overstated. ⁹ The genetic test for the BRCA gene mutation uses DNA analysis to identify mutations in either the BRCA1 or BRCA2 gene. ¹⁴ A positive BRCA test result indicates that a person has an increased risk of developing breast cancer; however, this result does not mean the person will develop breast cancer. ¹¹¹⁴

Certain social and ethical implications exist in considering genetic testing. Unlike other blood tests, genetic testing provides information not only about the patient but also about the patient's relatives which places an emotional burden on the patient with a positive test result.¹⁵ A positive test result may also place the person at risk for discrimination from health insurance companies. For example, a person with a positive test result may be denied insurance coverage related to the genetic condition.¹¹ Regardless of the test results, genetic testing is an emotional ordeal and the reaction of the patient must be considered.

SCREENING WOMEN WITH STRONG FAMILY HISTORY OR GENETIC PREDISPOSITION

The 23.5% decline in breast cancer mortality from 1990 to 2000 highlighted the importance of breast cancer screening as a part of a health maintenance program for women at average risk for breast cancer.⁴ However, inherited breast cancer typically occurs at a younger age and has a faster growth rate; therefore, for those at high risk, screening must be initiated earlier than standard recommendations.¹⁵ Primary care providers must determine the most appropriate breast cancer screening method for women identified with a genetic predisposition.

Women with a genetic predisposition to breast cancer should have an annual mammogram along with a clinical breast exam every 6 to 12 months. A periodic self breast exam is also recommended. Annual magnetic resonance imaging (MRI) is also recommended as an adjunct to the mammogram and clinical breast exam.⁹ The clinical breast exam, annual mammogram and breast MRI screening should begin at age 25 or on an individualized timetable starting 5 to 10 years prior to the youngest breast cancer case in the family.^{9,13} For women younger than the age of 25 with a genetic predisposition or strong family history, an annual clinical breast exams along with period self breast exams are recommended.⁹ These guidelines should also be applied to men testing positive for a BRCA mutation. For this population, a semiannual clinical breast examination and monthly self breast examination is recommended.⁹ A baseline mammography should also be considered and for men with gynecomastia or parenchymal/glandular breast density on the baseline screening, annual mammography screenings should be done. Men with this mutation should also follow population screening guidelines for prostate cancer.⁹

While these recommendations are based on studies

indicating that MRI is significantly more sensitive than mammography, the limitations of the MRI must be considered. One such limitation is that the MRI has a lower specificity than mammography and as a result, the MRI will generate more findings judged as suspicious. This increase in suspicious findings may result in a higher likelihood of referrals for breast biopsies.^{16,17} Therefore, the American Cancer Society recommends that decisions about screening options for women with BRCA1 and BRCA2 should be based on shared decision making between the health care provider and the patient after a review of potential benefits, limitations, and harms of the different screening strategies and the degree of uncertainty of each.¹¹³

CLINICAL MANAGEMENT OF WOMEN WITH GENETIC RISK FACTORS.

Chemoprevention may be considered for breast cancer risk reduction in women with a genetic predisposition to breast cancer. One such chemoprevention drug is tamoxifen. This drug reduces the risk for estrogen-receptor positive breast cancers.⁸ The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) have established recommendations for chemoprevention for the use of tamoxifen in women with a genetic predisposition of breast cancer; however, the risks and side effects must be carefully considered and discussed with each patient considering this form of treatment.^{9,14} The side effects of tamoxifen include hot flashes, risk of deep vein thrombosis, retinopathy, and cataract formations. Follow-up for patients desiring this form of chemoprevention is essential and should include ophthalmologic evaluation and routine gynecologic examinations.⁹ Discontinuation of tamoxifen is recommended prior to elective surgery and permanently for any patient who develops deep vein thrombosis, pulmonary embolus, or stroke.⁸

As preventative management, prophylaxis mastectomy is controversial. A preponderance of evidence exists to confirm that prophylactic mastectomy reduces the incidence of breast cancer in women with a BRCA mutation; however, no convincing evidence exists to indicate a positive effect on survival rates.^{13,18} The Society of Surgical Oncology has proposed guidelines to assist in considering prophylactic mastectomy; however, no absolute indications for this procedure have been identified.¹³ Health care providers must ensure that women who are candidates for this choice of management are carefully advised of the realistic breast cancer risk estimates.¹⁹

PROGNOSIS

Breast cancer must be diagnosed at the earliest possible stage in order to provide an optimal chance of survival. Studies have revealed that women with mutations in either BRCA1 or BRCA2 have a predicted lifetime risk of breast cancer between 37 to 85% and a lifetime risk of ovarian cancer between 15 to 49%. BRCA mutation carriers who have already been diagnosed with breast cancer have a 65% risk of developing a second primary breast cancer by the age of 70. ³ Women who are BRCA positive are also at an increased risk for a recurrence of breast cancer. ²⁰ Also of note is that BRCA alterations are associated with increased risks for additional cancer types that include pancreatic, fallopian tube, stomach, and colon cancers for BRCA1 and stomach, gallbladder, bile duct, pancreatic, and pharynx cancers for BRCA2. ²³

CONCLUSION

An estimated 5 to 10% of all breast cancers are inherited and the breast cancer susceptibility genes BRCA1 and BRCA2 have been identified as being responsible for 21 to 40% of these cases. Furthermore, women who carry a germline mutation in BRCA1 have a cumulative lifetime risk for developing breast cancer of 50 to 85%. ² Although several other breast cancer susceptibility genes have been identified, the genetic contribution to breast cancer development remains largely unknown. ⁷ With continued advancements in risk reduction options, including chemopreventive agents and increased surveillance, the ability to effectively reduce cancer risk has increased. Comprehensive genetic counseling that includes risk assessment, genetic testing, and surveillance and preventative strategies are essential for women who have been identified as being at high risk for inherited breast cancer.

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References

1. American Cancer Society. American Cancer Society guidelines for the early detection of cancer. 2008 April. Available from: URL: [http://www.cancer.org].
2. James CR, Quinn JE, Mullan PB, Johnston PG, Harkin DP. BRCA: A potential predictive biomarker in the

- treatment of breast cancer. *The Oncologist*. 2007; 12(2): 142-50.
3. Bradbury AR, Olopade OI. Genetic susceptibility to breast cancer. *Review of Endocrine Metabolism Disorders*. 2007; 8: 253-67.
4. Knutson D, Steiner E. Screening for breast cancer: current recommendations and future directions. *American Family Physician*. 2007; 75(1): 1660-66.
5. Olopade OL, Fackenthal JD, Dunston G, Tainsky MA, Collins F, Whitfield-Broome C. Breast cancer genetics in African Americans. *Cancer Supplement*. 2003; 97(1): 236-45.
6. Trent RJ. Introduction to genetics. *Molecular Medicine: An Introductory Text*. Elsevier; 2005. p. 213-18.
7. Oldenburg RA, Meijers-Heijboer H, Cornelisse CJ, Devilee P. Genetic susceptibility for breast cancer: How many more genes to be found. *Critical Reviews in Oncology/Hematology*. 2007; 63: 125-49.
8. Lippman ME. Breast Cancer. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill; 2005. p. 571-78.
9. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Genetic Familial High Risk Assessment: Breast and Ovarian Cancer. 2008. Accessed at www.nccn.org/professionals/physician_gls/PDF/genetics_screeening.pdf on 1 April 2008.
10. Satagopan JM, Offit K, Foulkes W, Wacholder S, Eng CM, et al. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev*. 2004; 10: 467-73.
11. Meiser B, Halliday JL. What is the impact of counseling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. *Social Science and Medicine*. 2002; 54: 1463-70.
12. Borry P, Stultiens L, Nys H, Diericks K. Attitudes towards predictive genetic testing in minors for familial breast cancer: a systematic review. *Critical Reviews in Oncology Hematology*. 2007; 64: 173-81.
13. United States Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: Recommendation statement. 2006 April. Available from: URL: [http://www.aafp.org].
14. American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility. Accessed at www.asco.org/asco/downloads/GeneticTesting.pdf on 1 April 2008.
15. Peshkin NF, Isaacs C. Evaluation and management of women with BRCA 1/2 mutations. *Oncology*. 2005; 19: 1451-59.
16. Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdejn IM. Efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition. *The New England Journal of Medicine*. 2004; 351(5): 427-37.
17. Morris E, Liberman L, Ballon DJ, Rubson M, Abramson AF, Heerdt A. MRI of occult breast carcinoma in a high risk population. *American Journal of Radiology*. 2003; 181: 619-26.
18. Zakaria S, Degnim AC. Prophylactic Mastectomy. *Surgical Clinics of North America*. 2007; 87: 317-31.
19. Sakorafas GH, Tsiotou AG. Genetic predisposition to breast cancer: A surgical perspective. *British Journal of Surgery*. 2000; 87: 149-162.
20. Tamer M, Russo D, Toxel A, Bernardino LP, Mazziotta R, Estabrook A. Survival and recurrence after breast cancer in BRCA1/2 mutation carriers. *Annals of Surgical Oncology*. 2004; 11: 57-164.

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