Archives of Surgical Research | Invited Commentary

Need For Genetic Testing And Counseling For Hereditary Breast Cancer

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IMPORTANCE Breast cancer is the commonest cancer among women and in many instances, it has a hereditary predisposition also. The commonest known genes associated with a familial predisposition of breast cancer are mutated BRCA1 and BRCA 2 which are located on chromosomes 17 & 13 respectively and are inherited in autosomal dominant fashion. All individuals suspected of having a familial predisposition for breast cancer should be subjected to genetic counseling, screening, and testing for BRCA 1&2 genes and if they come out to be positive then their relatives should be counseled and tested too so that safe surveillance and management options can be offered to them.

KEYWORDS Breast cancer, BRCA1 & BRCA2, genetic testing, genetic counseling, screening

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Invited Commentary

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Breast cancer is the commonest cancer among women and the second commonest cause of cancer-related deaths in women[1]. It is present in 1 in 8 women, thus 11% of families will have more than one patient with breast cancer. So it is a challenge to identify females from families having a genetic predisposition for breast cancer from women having sporadic disease due to clustering by chance without any familial predisposition. Although in the majority of cases, breast cancer is sporadic, genetic mutations are associated with 10-15% of the cases2. Nearly 25% of hereditary cases are due to mutation in BRCA1 and BRCA 2 genes which are inherited through autosomal dominant fashion on chromosomes 17 &13 respectively. BRCA mutations exhibit as hereditary breast/ovarian cancer syndrome. These BRCA carriers have an 82% lifetime risk of developing breast cancer and 10-40% risk of ovarian cancer for BRCA 1and 10-20% risk for BRCA 2. They also have a risk of developing fallopian tube, prostate, and pancreatic cancers[3].

DETECTION

BRCA 1 and BRCA 2 associated breast and ovarian cancer should be suspected in people with a personal or family history of the following:

- Breast cancer diagnosed at or before 50 years of age
- Ovarian carcinoma
- Multifocal uni/bilateral primary breast cancer
- Male breast cancer
- Triple-negative breast cancer (ER-ve, PR-ve, HER 2 neu-ve) especially when age is less than 60 years
- Combination of pancreatic and /or prostate with breast cancer
- Ashkenazi jew ancestry
- 2 or more relatives with breast cancer, one < 50years of age
- 3 or more relatives with breast cancer at any age
- Previous family history of BRCA1/BRCA2 [4,5]

SCREENING:

NCCN has issued recommendations for BRCA mutated breast cancer. Surveillance includes monthly self-breast examination, clinical breast examination, annual mammograms, and annual MRI of the breast. These yearly mammograms will start at 25 years of age. MRI is more sensitive than a mammogram in the detection of early-onset breast cancer in young female[7].

RISK ASSESSMENT:

Mutations in BRCA 1&2 genes are familial. Several risk assessment tools have been devised that include patient age at disease onset, gender, age at death, family history of affected members, type of cancer present in patients or relatives. The tools evaluated by USPSTF include Ontario family history assessment tool, Manchester scoring system, Referral screening tool, Pedigree assessment tool,7 Question family history screening tool, International breast carcinoma intervention study instrument, and BRCAPRO. Each of them accurately estimates the risk of carrying BRCA 1&2 mutation [6,8]. These tools help us to assess and refer the patient for genetic counseling for a better risk assessment[8]. The above recommendations clearly define the population to consider for testing[6].

Table 1: The recommendations by US preventive services task force are:

Assessment of risk, Genetic Counseling, and Genetic Testing for BRCA-Related hereditary Cancer: Clinical Summary of the USPSTF Recommendation		
Population	Women population with a personal or family history of breast, ovarian, peritoneal, or tubal cancer or having an ancestry associated with BRCA1/2 gene mutations	Women whose personal or family history or ancestry is not associated with harmful BRCA1/2 gene mutations
Recommendation	Assess with a brief familial risk assessment tool.	Routine risk assessment not needed
Risk assessment	Risk assessment of patients with family or personal history of breast, ovarian, tubal, or peritoneal cancer or ancestry associated with harmful BRCA1/2 mutations should be done using a familial risk assessment tool. The USPSTF found that these tools are accurate .Tools evaluated by the USPSTF include the Ontario Family History Assessment Tool System, Referral Screening Tool, Pedigree Assessment Tool, , Manchester Scoring , International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), 7-Question Family History Screening Tool, and BRCAPRO. Referrals to genetic counseling should be made based on these tools.	
Genetic counseling	Genetic counseling about BRCA1/2 mutation testing to be done by trained health professionals. The process of genetic counseling consists of family analysis and risk assessment for BRCA1/2 mutations and identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results, and discussion of management options.	
Genetic testing	A person should be tested for BRCA1/2 mutations when she/he has personal or family history that suggesting an inherited cancer susceptibility, when an individual is willing to see a trained genetic counselor and when test results will help in decision making.	
Treatment and interventions	Women with harmful BRCA1/2 mutations are managed with different interventions to lower future risk of cancer. This includes screening, medications, and mastectomy and salpingo-oophorectomy.	
Other relevant USPSTF recommendations	The USPSTF recommends use of medications such as tamoxifen, raloxifene, or aromatase inhibitors to women at increased risk for breast cancer. The USPSTF does not recommend for screening for ovarian cancer. This recommendation does not apply to women with known BRCA1/2 mutations.	
Note: For a full recommendation statement, and supporting documents, go to https://www.uspreventiveservicestaskforce.org/. USPSTF = U.S. Preventive Services Task Force		

GENETIC COUNSELING:

It can provide the patient the lifesaving info. Pretest counseling is performed by a genetic counselor, medical or surgical oncologist, or health professional with sufficient knowledge of cancer genetics 9. The patient should be informed about the implications of a positive, negative, or inconclusive (VUS) result. It decreases stress and improves risk perception[10]. Genetic counseling for VUS is complex because we have no guidelines about how to disclose variants of unknown significance (VUS). National society of genetic counseling NSGC indicates that counselors should discuss VUS with patients during pretest counseling and during post-test counseling if VUS is found[11].

GENETIC TESTING:

Genetic testing for BRCA 12 is performed only if

• the individual has a personal/family history suggestive of hereditary breast cancer

• the patient is willing to talk to a genetic counselor

• Results will help in decision making and future surveillance and management plans6

This testing can impact multiple family members beyond the one being tested. If the test result is positive, unaffected family members also need to be tested for the presence of the mutant gene for screening and surveillance. But there can be a lack of willingness by family members for this testing [12, 13].

TREATMENT AND PREVENTION:

Three main options are:

• Prophylactic mastectomy:

It is the most effective way to prevent BRCA associated breast cancer. It eliminates the risk for metastatic spread and death. Offers 80% risk reduction. Total mastectomy is preferred over subcutaneous or nipple-sparing mastectomy [14,15]

• Prophylactic oophorectomy

As BRCA 1 is associated with hormones, oophorectomy blocks the effect of ovarian estrogen thus reducing the risk of BRCA 1 associated cancer [16]

• Chemoprevention

By selective estrogen receptor modulators like Tamoxifen/Raloxifene [15,16]

Routine screening (secondary prevention) to detect early cancer [16].

FUTURE GOALS

Till now screening is being offered to those who are thought to have susceptibility to develop BRCA associated

cancer. This may miss a large chunk of the asymptomatic population. Since the cost of genetic panel testing has markedly fallen now so screening for BRCA 1& 2 should be offered to all patients with breast cancer.

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