INHERITED MUTATION IN BRCA1 AND BRCA2 IN BREAST CANCER

Diksha Mishra¹, Savita Kumari², Navneeta R. Kumar³

¹Assistant Professor, Quadra Institute of Medical Science.

²Lecturer, Sarjug Dental College and Hospital, Darbhanga

³Vice Principal, Quadra Institute of Medical Science.

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Address for Correspondence: Diksha Mishra

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Abstract

BRCA1 and BRCA2 are unrelated proteins, but both are normally expressed in the cells of breast and other tissue, where they help repair damaged DNA, or destroy cells if DNA cannot be repaired. They are involved in the repair of chromosomal damage with an important role in the error-free repair of DNA double-strand breaks. If BRCA1 or BRCA2 itself is damaged by a BRCA mutation, damaged DNA is not repaired properly, and this increases the risk for breast cancer. BRCA1 and BRCA2 have been described as "breast cancer susceptibility genes" and "breast cancer susceptibility proteins". The predominant allele has a normal, tumor suppressive function whereas high penetrance mutations in these genes cause a loss of tumor suppressive function which correlates with an increased risk of breast cancer.

Keywords: BRCA1; BRCA2; Breast cancer; Mutation; Gene.

1. Introduction:

BRCA1 and BRCA2 are human genes that produce tumor suppressor proteins. These proteins help repair damaged DNA and, therefore, play a role in ensuring the stability of each cell's genetic material. When either of these genes is mutated, or altered, such that its protein product is not made or does not function correctly, DNA damage may not be repaired properly. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer.(1)

Breast cancer: About 12% of women in the general population will develop breast cancer sometime during their lives (1). By contrast, a recent large study estimated that about 72% of women who inherit a harmful BRCA1 mutation and about 69% of women who inherit a harmful BRCA2 mutation will develop breast cancer by the age of 80 (2).

2. Genetic test:

Different tests are available. Some tests look for a specific harmful BRCA1 or BRCA2 gene mutation that has already been identified in another family member. Other tests check for all of the known harmful mutations in both genes. Multigene (panel) testing uses next-generation sequencing to look for

harmful mutations in many genes that are associated with an increased risk of breast and ovarian cancer, including BRCA1 and BRCA2, at the same time.

DNA (usually from a blood or saliva sample) is needed for all of these tests. The sample is sent to a laboratory for analysis. It usually takes about a month to get the test results.

Testing for BRCA1 and BRCA2 mutations is expensive (currently the cost is \$2,400 for both genes), and a positive outcome can affect a person's life in important ways: in eligibility for health insurance and in potential employment discrimination, as well as in physical and psychological aspects. A positive test or simply the perception of a high risk can lead to aggressive management, ranging from more-frequent mammographies to bilateral mastectomy, again with substantive consequences on a woman's life. A crucial step in counseling a women facing these decisions is an accurate evaluation of the probability that she carries a mutation. Also, after the test(s) is performed, the relevant calculation for decision making is the posterior probability of mutation, given the outcome of the test. Accurate assessment of these probabilities requires accurate prior input.

3. Prevalence of BRCA1 and BRCA2 mutations in breast cancer

The BRCA1 and BRCA2 gene mutations, on chromosomes 17 and 13, respectively, account for the majority of autosomal dominant inherited breast cancers. Both genes are believed to be tumor suppressor genes whose transcribed protein products are involved with maintaining DNA integrity and transcriptional regulation.

4. Inheritance of a mutant BRCA1 or BRCA2 gene:

Numbers 113705 and 600185, respectively, in Online Mendelian Inheritance in Man, a catalogue of inherited diseases confers a lifetime risk of breast cancer of 50 to 85 percent and a lifetime risk of ovarian cancer of 15 to 45 percent. These germ-line mutations account for a substantial proportion of inherited breast and ovarian cancers, but it is likely that additional susceptibility genes will be discovered.

Breast cancer is the most common malignancy and the leading cause of cancer-related deaths among Jordanian women. With a median age of 50 years at diagnosis, a higher prevalence of hereditary breast cancer may be expected. The objective of this pilot study is to evaluate, for the first time, the contribution of germline mutations in BRCA1/2 to breast cancer among Jordanian patients.

5. BRCA1 and BRCA2 Mutations:

To some extent, the types of mutation that have been reported reflect the ease with which they are detected and the unambiguous nature of their effects on the BRCA1 protein. For this reason, most of the mutations that were first reported result in protein truncations; these are either small insertions or deletions, or are nonsense mutations that lead to the introduction of a stop codon. These mutations invariably generate a shortened, non-functional BRCA1 protein.

Hereditary Breast and Ovarian Cancer syndrome (HBOC) is caused by mutations in one of two genes: BRCA1 or BRCA2. Women with HBOC have a high risk for both breast and ovarian cancer. Men with HBOC have an increased risk for breast cancer and prostate cancer. Both men and women with HBOC may have an increased risk for melanoma and pancreatic cancer. Sometimes, these cancers can develop at young ages.

Figure 1: Location of Mutation in BRCA2 Gene

5.1 Functions of BRCA1 and BRCA2:

Not all of the functions of the BRCA1 and BRCA2 proteins have been established, although many have been discovered during the past decade. BRCA2 is the larger of the two proteins and consists of 3,418 amino acids (FIG. 1). BRCA2 is involved in homologous recombination, but little else is known about its function. By contrast, several known functions of BRCA1 might underlie its role in carcinogenesis. These roles include DNA repair, cellcycle-checkpoint control, protein ubiquitylation and chromatin remodeling.

Figure 2: Functions of BRCA1 and BRCA2

5.2 Pathology:

In 1993, the Breast Cancer Linkage Consortium (BCLC; see online links box) was created to facilitate collaborative breast cancer linkage studies. Admirably, the group stayed together following the cloning of the BRCA genes and has facilitated many clinical and pathological studies. Through the work of the BCLC and other groups, a clinicopathological phenotype for BRCA1-related breast cancer has emerged (TABLE 120)

2). Sobol and colleagues have suggested that these features are sufficiently specific that they can be used to identify probable carriers, based on tumour pathology. BRCA1-related breast cancers are usually high-grade infiltrating ductal carcinomas. An atypical medullary phenotype (which is characterized by syncytial growth patterns, a smooth margin and abundant lymphocytic infiltration) is more common in BRCA1-related breast cancer than in matched controls but occurs in only ~10% of BRCA1-related tumours. Conventional and molecular karyotyping studies have shown that the cells of these tumours are usually highly disorganized. They are also usually ER-negative, particularly in younger women. Notably, the receptor tyrosine kinase ERBB2 (also known as HER2 or NEU) is overexpressed less often, compared with age-matched controls. Many other immunohistochemical markers have been studied, most in small series.

Figure 3: BRCA 1/2 Tumors and Gene Expression Therapy for Breast

6. Penetrance:

The penetrance of BRCA mutations is still a matter of intense research 10 years after the discovery of these genes (BOX 2). It is likely that more effort has gone into estimating the penetrance of BRCA1 mutations than for mutations of any other gene. This investment is rational, given the high frequency of mutations and the obligation to communicate risk with accuracy prior to offering drastic preventive options, such as prophylactic mastectomy. It is perhaps disappointing that there is still controversy regarding which estimates of penetrance should be used to counsel women with BRCA1 and BRCA2 mutations; however, it is probably not surprising, as different studies continue to generate different figures. Penetrance — the lifetime risk of developing

breast or ovarian cancer — is usually defined as the risk up to the age of 70 years.

7. Conclusion:

A BRCA mutation is a mutation in either of the BRCA1 and BRCA2 genes, which are tumour suppressor genes. Hundreds of different types of mutations in these genes have been identified, some of which have been determined to be harmful, while others have no proven impact. Harmful mutations in these genes may produce a hereditary breast-ovarian cancer syndrome in affected persons. Only 5-10% of breast cancer cases in women are attributed to BRCA1 and BRCA2 mutations (with BRCA1 mutations being slightly more common than BRCA2 mutations), but the impact on women with the gene mutation is more profound.

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