Hereditary Breast Cancer: A Brief Overview

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Abstract

Introduction: *Breast cancer, one of the most common and serious malignancies affecting women, occurs in sporadic and hereditary forms. The recent identification of breast cancer predisposing genes involved in the aetiology of breast cancer has provided us with new insights into this field.* ***Methods:*** *In order to understand the molecular basis of familial breast cancer, English literature identified through Medline between 1995 and February 2000 were reviewed using the search terms: breast cancer, genetics, hereditary,* **BRCA1** *and* **BRCA2,** *amongst others.* ***Results:*** *In this brief overview, some of the advances in the aetiology of breast cancer will be highlighted. This overview is divided into the following categories: cancer genes, inherited genetic predisposition to breast cancer,* **BRCA1** *and* **BRCA2.**

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Introduction

Worldwide, breast cancer is the third most common form of cancer, after lung and stomach cancer, and it is the most common form among women.[1] The age-adjusted incidence rates of breast cancer are 176% higher in developed than developing countries.[2] In Singapore, the incidence of breast cancer has doubled over the past 20 years with an annual increase significantly higher in premenopausal than postmenopausal women (5.7% versus 3.9%).[3] Of note, this annual increase in premenopausal Singaporean Chinese women is almost 4-fold higher when compared to cancer incidence rates from Western countries.[4] Over the last five years, various determinants of breast cancer occurrence have been postulated and these have included diet,[5,6] reproductive factors,[7,8] anthropometry,[9-11] endogenous and exogenous hormones,[12] and mammographic density,[13] amongst others. This article presents a brief overview on the genetic determinant with emphasis placed on the genes involved in breast cancer susceptibility.

Cancer Genes

The genes that play a major role in the development of cancer are divided into two broad classes, the oncogenes and the tumour suppressor genes. Proto-oncogenes, the normally functioning cellular counterparts of viral oncogenes, have essential roles in diverse signalling pathways that regulate embryonic development, cell renewal in adult tissues, differentiation and apoptosis. Mutations such as point mutations, chromosomal translocation and gene amplification can deregulate their expression and/or alter their structure, resulting in increased or novel functions of the protein product. These defects are often referred to as gain-of-function or activating mutations. By contrast, tumour suppressor genes are targeted by loss-of-function mutations in cancer cells and are often identified by the presence of germline mutations that predispose individuals to inherited forms of cancer and by the study of chromosome losses in tumours.[14] Like oncogenes, tumour suppressor genes have diverse functions such as growth regulation, differentiation and programmed cell death. Examples of oncogenes that have been found to be associated with breast cancer are *HER-2/neu* (*c-erb-B2*) and *CYCD1*. Selected tumour suppressor genes shown to be involved in breast cancer are *p53*, *RB1*, and the breast cancer susceptibility genes *BRCA1* and *BRCA2*.

Inherited Genetic Predisposition to Breast Cancer

Breast cancer occurs in hereditary and sporadic forms. Although the majority of breast cancer arise from acquired genetic (sporadic) mutations, inherited (familial) mutations make up about 5% to 10% of all cases. A family history of breast cancer is recognised as one of the most important risk factors for the disease. In the majority of patients from families with breast cancer, this risk may represent a multifactorial combination of environmental factors and genetic input, but in some cases, it is the direct result of a dominant genetic influence. Hence, given the high frequency of this disease, a large number of women are genetically

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predisposed to the development of breast cancer.

Two main classes of inherited susceptibility genes in the aetiology of beast cancer may now be considered. First of all, there are genes with relatively common disease-associated variant allele frequencies that confer low to moderate breast cancer risk to individuals although molecular epidemiological studies have yet to provide clear-cut evidence for these polygene-breast cancer associations. Examples of these candidate genes include: *HRAS1*,[15] glutathione S-transferases *GSTT1*, *GSTM1* or *GSTP1*;[16,17] members of the cytochrome P-450 multigene family such as *CYP1A1*, *CYP2D6* or *CYP17*;[18] the N-acetyltransferases *NAT1* and *NAT2*;[18] DNA repair genes such as *ATM* (a gene mutated in ataxia telangiectasia);[19] *ER* (estrogen receptor) gene[20,21] and *COMT* (catechol-O-methyltransferase) gene,[22,23] amongst others. Few, if any, of these polygenes have been associated with breast cancer aetiology by themselves and most positive associations have been made in conjunction with other risk factor(s) for breast cancer such as exogenous oestrogen, diet, cigarette smoking and other environmental exposures.

Secondly, there are the major genes with allelic variants that confer a high degree of risk to the individual, a hallmark of which is the creation of a Mendelian, and often autosomal dominant, pattern of cancer. These genes, which are relatively few in number, also tend to predispose to:

a) earlier onset, with as many as 30% of women developing breast cancer before the age 35 having inherited susceptibility, and less than 1% of women being diagnosed after age 75 having breast cancer associated with a dominant susceptibility gene;
b) an excess of bilateral disease; and
c) an association with other malignancies. Examples of the major genes that have been identified to date include *TP53* (Li-Fraumeni syndrome),[24,25] *PTEN* (Cowden syndrome),[26,27] *MSH2/MLH1* (Muir-Torre syndrome)[28] and *STK11* (Peutz-Jeghers syndrome).[29] Although mutations in these genes explain a very small population of breast cancer in the general population, the risk conferred by the variants of these genes is generally high.

In contrast to the above-mentioned genes and their rare syndromes, germline mutations in the tumour suppressor genes *BRCA1* and *BRCA2* explain a relatively large proportion of hereditary breast cancer in the population. Ford et al[30] have estimated that mutations in *BRCA1* and *BRCA2* account for 52% and 32% of hereditary breast cancer respectively, with the remainder being accounted for by one or more yet unidentifiable gene.

BRCA1 and BRCA2

The breast/ovarian cancer susceptibility genes *BRCA1* and *BRCA2*, localised on chromosome 17q12-21 and 13q12-13 respectively, are tumour suppressor genes that are involved in familial predisposition to breast cancer.[31-35] Germline mutations in these genes are considered to be responsible for up to 80% of familial breast cancer cases, rendering them high penetrance genes. In addition to breast cancer, germline mutations in *BRCA1* also predispose individuals to ovarian cancer,[36-38] whereas *BRCA2* mutations are implicated in male breast[39] and pancreatic[40] cancers, amongst others.

Mutation spectrum: The spectrum of disease-associated mutations in various populations has been investigated in detail over the last 5 years, with more than 350 different germline mutations in *BRCA1* clearly associated with cancer susceptibility, registered in the Breast Cancer Information Core (BIC) database (http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic). In addition, more than another 100 such mutations have now been registered for *BRCA2*. These sequence variants have been shown to be distributed along the entire coding regions of both *BRCA1* and *BRCA2* which indicate that in most settings, a *BRCA1* or *BRCA2* mutation test must evaluate the entire coding region of the gene. The majority of studies have revealed that most of these mutations generate stop codons, truncating the protein product leading to a loss-of-function. These deletions and insertions, leading to frame-shift and nonsense mutations, constitute about 60% of all mutations in *BRCA1* and 80% of all mutations in *BRCA2*. In addition, mutations have also been found in the signals that normally allow proper splicing of the mRNA, or as single base substitutions, thus destroying a functional domain of the protein.

Consequently, as a result of these epidemiological studies, a few common mutations have now been identified in *BRCA1* and *BRCA2*, particularly in specific subpopulations. This phenomenon is most likely to occur in populations that have historically been geographically or politically isolated from surrounding populations, in which reproduction occurs solely within the group. Another factor is the absence of selection bias before childbearing age, such that most mutation carriers reproduce before succumbing to breast or ovarian cancer. This common ancestry of a mutation may be shown by haplotyping and reveals founder effects in the subpopulation. Such founder mutations for *BRCA1* and *BRCA2* have now been described in Ashkenazi Jews[41-43] and reported for the Icelanders,[44] Dutch,[45,46] Norwegians,[47] Finns,[48] Swedes,[49] Russians,[50] French Canadians,[51] Japanese[52] and African Americans.[53] Another interesting observation that has arisen from these epidemiological studies is the apparent occurrence of genotype-phenotype correlation with respect to a specific *BRCA1* or *BRCA2* mutation and the risk of breast and

ovarian cancers. Gayther et al[37] proposed that the presence of a truncating mutation in the first two-thirds of *BRCA1* instead of in the last third of the gene may significantly increase the risk of ovarian cancer in comparison with that of breast cancer. Likewise, mutations leading to a truncated *BRCA2* protein in families with the highest risk of ovarian cancer were all found to be clustered in a region of about 3.3 kb in exon 11.[54] Controversy still exists however, over whether the locality of the mutation within *BRCA1* plays a role in the clinical appearance in the family or individual, as several larger studies have since failed to reproduce this finding. It may be, as suggested by Sobol et al,[55] mutations that occur in the terminal regions of *BRCA1* are associated with a more severe phenotype, as defined by a higher breast tumour grade.

BRCA1 and BRCA2 protein function: The products of both *BRCA1* and *BRCA2* are large nuclear proteins; the *BRCA1* gene encodes a protein of 1863 amino acids, the *BRCA2* gene a protein of 3418 amino acids. Their primary amino acid sequences have revealed little information regarding the function of these genes and, although there are some similarities between their genetic structure, there is no sequence homology between them. When *BRCA1* was isolated, a RING finger domain (containing the zinc finger motif) was identified near the NH_2-terminus. This RING finger is found in several proto-oncoproteins, regulatory and transcription factors[56] and although a well-defined function has not been identified, it appears to interact with DNA, either through direct binding or indirectly by mediating protein-protein interactions.[57] This finding suggests that *BRCA1* might be a transcription factor and since then, recent studies have also indicated that it is possible that *BRCA1* encodes a transcription factor with an NH_2-terminal DNA and protein binding domain and a COOH-terminal domain with transactivational activity.[58-65] Of *BRCA1*'s role during normal tissue development and tumour progression, studies also indicate that a certain amount of normally functioning *BRCA1* is required for the maintenance of negative growth regulatory mechanisms in mammary epithelial cells; and that breast cancer may arise either through the disruption of *BRCA1* function or through a decrease in relation to *BRCA1* expression.[66-69]

Although the molecular mechanism of action of *BRCA1* and *BRCA2* remains largely undefined, evidence is now accumulating that they might be involved in transcriptional regulation.[70,71] More recently, other groups have provided insight that these genes may be components of DNA damage response pathways from their interactions with human Rad51. Rad51, the eukaryotic equivalent of the bacterial recombination protein recA, is a major participant in eukaryotic double-strand break repair and homologous recombination. It has been shown that *BRCA1* colocalises and interacts physically with Rad51 in both mitotic and meiotic cells, suggesting a role for *BRCA1* in the control of DNA recombination and of genome integrity.[72-77]

Clinical testing: Direct sequencing is now believed to be the most sensitive and specific *BRCA1* and *BRCA2* mutation testing available; however, it is the most expensive mutation detection technique due to the large size of these genes and the technique being labour-intensive. Gel shift assays, such as single-strand conformation-sensitive polymorphism and the multiplex heteroduplex analysis, reduce the number of samples that must be sequenced but the sensitivity of these assays are variable.[78-80] Other assays, such as allele specific oligonucleotide (ASO) hybridisation and protein truncation test (PTT) are available but, have the limitation of identifying only specific mutations.[81,82] Hence, new technologies are being developed in order to improve the efficiency of mutation testing, reducing the cost of testing and enabling population-based studies of mutation prevalence and disease penetrance to be conducted.

In the setting of clinical testing, two main categories of mutation test results may be difficult to interpret. First of all, missense mutations that do not always result in an altered function of the protein product. These mutations are not located within the functional domains and are not likely to be disease associated. Hence, determination of the functional significance of newly-identified missense mutations outside of the RING finger domain of *BRCA1* and *BRCA2* requires clear correlation with the disease status in multiple affected families and individuals. Secondly, the difficulties in interpreting a negative test result, particularly from an affected member of a family with high probability of carrying the breast cancer susceptibility gene mutation. Most routinely available tests fail to identify up to 10% of the mutations in both *BRCA1* and *BRCA2* that occur in a non-coding region, which results in a false-negative result. Finally, as more information becomes available, caution must be exercised especially when counselling all individuals about specific risks, especially non-Caucasian persons who have, apart from recent studies on the Japanese and Chinese,[52,83-85] been poorly represented in most genetic epidemiological studies.

In summary, new studies are continuously being presented that address the genetic aetiology of beast cancer. Despite this progress, some of the more complex issues of breast cancer aetiology still remain unresolved. These issues include the interactions between risk genes and environmental factors, the role of specific low penetrance genes and the existence of aetiologic heterogeneity of breast cancer. By understanding and addressing these issues, improved diagnosis and potential for targeted cancer prevention strategies may be possible.

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