Review

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Genetic Basis of Breast Cancer

Pathology Section

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ABSTRACT

Breast cancer is the commonest cancer in women worldwide. Today, there is no woman in the world who is at a truly low risk of developing the disease. In India, the growing epidemic of breast cancer presents a major challenge to the global public health, especially, given the failure to cope with the current situation. The burden of breast cancer will continue to increase, not only in terms of the absolute number of cases, but also in terms of its incidence. It has long been observed that 5 to 10% of the breast cancers are the result of an inherited familial predisposition. So, the precise knowledge of the underlying genetic processes is useful for the early detection and prevention of breast cancer. As mammography will be difficult to be implemented in India for various reasons and also because of its complex nature and high cost, genetic testing is not presently routinely available in India. So, efforts should be made to detect breast cancer at an early stage by educating the people about the risk factors and screening methods like Breast Self Examination, because late stage presentation is the main problem in India, which leads to a poorer prognosis. In this review, the risk factors for the development of breast cancer, the role of various genes in the pathogenesis of breast cancer, the possible options for high risk women and the socio-cultural issues regarding breast cancer have been outlined.

Key Words: Breast cancer, genetics, risk factors, BRCA1

INTRODUCTION

What is Cancer?

Cancer is sometimes caused by alterations in the genes and / or in the expression of genes. The gene mutations in most of the cancers arise in the somatic cells and they are transmitted to the successive generations of cancer cells. In about 5-10% of the cancers, the disease is transmitted from a parent to the offspring. Such types of inherited cancers are rare. Approximately 50 heritable cancer syndromes are known. These syndromes provide an opportunity to understand the genetic basis of cancers and the role of various genes in their pathogenesis.

As the cell divides and re-divides, more and more genes get mutated, thus providing the cell with the potential to become more malignant. Thus, the development of a cancer is a multistage process.

What is Breast Cancer?

The term “breast cancer” refers to a malignant tumour that has developed from cells in the breast. Usually, breast cancer either begins in the cells of the lobules, which are the milk-producing glands, or in the ducts, the passages that drain milk from the lobules to the nipple. Less commonly, breast cancer can begin in the stromal tissues, which include the fatty and fibrous connective tissues of the breast.

Why Breast Cancer is Important?

The incidence of breast cancer in India is on the rise and it is rapidly becoming the number one cancer in females, pushing cervical cancer to the second spot. The seriousness of the situation is apparent from the recent data from the Indian Council of Medical Research (ICMR), where it is reported that one in twenty two women in India is likely to suffer from breast cancer during her lifetime , while the figure is definitely more in America, with one in eight women being the victims of this deadly type of cancer [1].

World: It has been estimated that about 9 million new cancer cases are diagnosed every year and that over 4.5 million people die from cancer each year in the world. The worldwide incidence of breast cancer comprises 10.4% of all the cancer incidences among women, making it the second most common type of non-skin cancer (after lung cancer) and the fifth most common cause of cancer death [2]. In 2004, breast cancer caused 5,19,000 deaths worldwide (7% of all the cancer deaths and almost 1% of all the deaths) [3]. Breast cancer is about 100 times more common in women than in men, although males tend to have a poorer outcome due to delays in the diagnosis [4].

India: The estimated number of new cancers in India per year is about 7 lakhs and over 3.5 lakhs people die of cancer each year. Out of these 7 lakhs new cancers, about 2.3 lakhs (33%) cancers are tobacco related. The data from the National Cancer Registry Program shows that in all the urban areas of India, breast cancer has now surpassed cervical cancer as the most frequently diagnosed cancer in women. The most recent data which was available from the National Cancer Registry Program showed a wide variation in the age standardized incidence rates which were observed between the rural and urban populations, which ranged from 36.1 in Bangalore to 7.2 in the Sikkim state. The age standardized mortality rate for breast cancer in India is 11.1 per 100000 (12.5 per 100000 globally). As in other developing regions, the mortality rates for breast cancer in India are high in comparison to its incidence rates. A poor survival may be largely explained by the lack of or limited access to the early detection services and treatment.

Risk Factors

The causes of the growing breast cancer epidemic are complex and are not well understood, which makes finding ways to prevent breast cancer elusive. Many experts blame the "westernization" of the developing world. "Westernization" has many positives, for it brings an increased life expectancy, an improved socio-economic status, and greater freedom for women. But it also has some negatives: changes in the diet and as more women take up sedentary jobs, less exercise, early menarche, delayed childbirth, families with fewer children, less breast feeding, and hormone replacement therapy – all are thought to increase the risk of breast cancer. The reasons for the recent observed increase in the incidence of breast cancer in the Indian population are not clearly understood, but it has been thought to be largely explained by the 'westernization' of the lifestyles and changes in the reproductive behaviour. There is no way for us to prevent breast cancer, but we can definitely detect it early and treat it adequately. Achieving this in a society will lead to a better "long-term" survival as well as a better quality of life.

The risk factors for developing breast cancer are sex , age or lack of childbearing or breast feeding [5] and higher hormone levels. "We used to think that breast cancer was a problem of only wealthy women, but now we know that breast cancer shows no favorites: It strikes the rich and the poor women alike," says Felicia Knaul, Ph.D., who heads the Harvard Global Equity Initiative and has produced a body of research on the issue. The big difference is that by the time the disease is diagnosed in poor women, it is often too late for effective treatment, which is the main problem in India.

Genetic factors usually increase the risk slightly or moderately. The exception is women and men who are carriers of the BRCA mutations. These people have a very high lifetime risk for breast and ovarian cancers, depending upon the portions of the proteins where the mutation occurs. Generally, hereditary breast cancers are earlier in onset and they have a higher prevalence of bilateral breast cancer. Genetics has transformed the use of the family history into and it has led to the reemergence of the detailed family history. It is critical that public and professional educational efforts increase the family history awareness and that they facilitate some of the limitations which are associated with the conventional maternal history ascertainment, ultimately improving the health care and research. The increasing use of genetic screening promises to cultivate a paradigm shift in the medical treatment, emphasizing on primary prevention and an early intervention. Appreciation of the history is necessary to make this important advance. The literature has described that a familial association for breast cancer is very extensive. With reports of individual pedigrees and numerous case control studies, most investigators have found a 2-3 fold increase in the risk of breast cancer among the relatives of breast cancer probands as compared to women in the matched control samples or in the general population.

Genetic Basis of Breast Cancer

Breast cancer is a genetic disease which is caused by an alteration in the genes or in the expression of the genes. Cell division and cell death are governed by several genes which are known to cause cancers.

The functions of proteins which are coded by genes which are implicated in cancers :

- A signaling pathway for cell proliferation
- Cytoskeletal components which are involved in the maintenance of contact inhibition
- Regulation of the cell cycle
- Programmed cell death (apoptosis)
- DNA repair mechanisms

Families which are at a high risk need a closer surveillance for the cancer of the breast. Mutation detection in these families helps in the definitive identification of the carrier and thus, in the identification of the subjects who require a close "follow-up" and also those who do not.

Genes for Breast Cancer

BRCA1 (breast cancer1, early onset) is a human tumour suppressor gene which produces a protein called the breast cancer type 1 susceptibility protein. It is found in the cells of breast and other tissues, where it helps in repairing damaged DNA and in destroying the cells when their DNA cannot be repaired. If BRCA1 itself is damaged, the damaged DNA can let the cell duplicate without control, and this can turn into a cancer.

The protein which is encoded by the BRCA1 gene combines with other tumour suppressors, DNA damage sensors, and signal transducers to form a large multi-subunit protein complex which is known as the BRCA1-associated genome surveillance complex (BASC) [6]. The BRCA1 protein associates with RNApolymerase II, and through the C terminal domain, also interacts with the histone cyclase complexes. This protein thus plays a role in the transcription DNA repair of double-stranded breaks, ubiquitination, transcriptional regulation, as well as other functions [7].

Gene Location

The human BRCA1 gene is located on the long (q) arm of chromosome 17 at band 21, from base pair to 38,530,994 (map). BRCA1 orthologs have been identified in most mammals, for which the complete genome data are available.

Protein Structure

The BRCA1 protien (breast cancer type 1 susceptibility protein which is also known as the RING finger protein 53) contains the following domains:

- Zinc finger, C3HC4 type RING FINGER pfam00097
- BRCA1 C Terminus (BRCT) domainPfam Pf 0053

This protein also contains the nuclear localization signal and the nuclear export motif signal.

Recent research has suggested that both the BRCA1 and the BRCA2 proteins regulate the activity of other genes and that they play a critical role in the embryo development. The BRCA1 protein probably interacts with many other proteins, including tumour suppressors and regulators of the cell division cycle.

Mutations and cancer risk

Certain variations of the BRCA1 gene can lead to an increased risk for breast cancer. Researchers have identified hundreds of mutations in the BRCA1 gene, many of which are associated with an increased risk of cancer. Women who have an abnormal BRCA1 or BRCA2 gene have up to an 85% risk of developing breast cancer by the age of 70; an increased risk of developing ovarian cancer is about 55% in women with BRCA1 mutations and about 25% in women with BRCA2 mutations.

These mutations can be changes in one or a small number of DNA base pairs (the building blocks of DNA). These mutations can be identified by PCR and DNA sequencing.

In some cases, large segments of DNA are rearranged. These large segments, also called as large rearrangements, can be a deletion or a duplication of one or several exons in the gene. The classical methods for mutation detection (sequencing) cannot reveal these mutations [8]. Other methods which have been proposed: Q-PCR, Multiplex Ligation–Dependent Probe Amplification (MLPA) and Quantitative Multiplex PCR of Short Fluorescent Fragments (QMPSF). Newer methods have been recently proposed: heteroduplex analysis (HDA) by multi-capillary electrophoresis and also, the dedicated oligonucleotides array based on comparative genomic hybridization (array-CGH). Some results have suggested that the hypermethylation of the BRCA1 promoter which has been reported in some cancers, could be considered as an inactivating mechanism for the BRCA1 expression.

A mutated BRCA1 gene usually makes a protein that does not function properly because it is abnormally short. Researchers believe that the defective BRCA1 protein is unable to help in fixing the mutations that occur in other genes. These defects accumulate and may allow the cells to grow and divide uncontrollably to form a tumour.

In addition to breast cancer, mutations in the BRCA1 gene also increase the risk on ovarian, fallopian tube and prostate cancers. Moreover, precancerous lesions (dysplasia) within the fallopian tube have been linked to the BRCA1 gene mutations. Pathogenic mutations anywhere in a model pathway containing BRCA1 and BRCA2 greatly increase the risks for a subset of leukaemias and lymphomas.

The BRCA2 gene is located on the long (q) arm of chromosome 13 at position 12.3 (13q12.3), from base pair 31,787,616 to base pair 31,871,804 [9]. It is composed of 27 exons and it encodes a protein of 3418 amino acids. The types of mutations which are related to it are frameshift mutations (68%), nonsense mutations (12%), splice sites (7%) and missense mutations (13%).

Other Breast Cancer Genes

The TP53 gene: This gene is located on the short arm of the chromosome 17. It is a tumour suppressor gene. Germline mutations of TP53 account for over 70% of the cases of the Li – Fraumeni syndrome. The Li – Fraumeni syndrome is an autosomal dominant cancer syndrome. Families with the Li – Fraumeni syndrome are at a high risk for soft tissue childhood sarcomas, breast cancers, brain tumours, and adrenal cortical tumours. TP53 accounts for a very small proportion of breast cancers outside the Li – Fraumeni syndrome.

The ATM gene: Hetrozygote carriers of the ataxia telangiectasia gene are known to be at a five fold risk for breast cancer. It is located on chromosome 11q.

The PTEN gene: Cowden disease is a rare autosomal dominant syndrome in which the affected members tend to develop bilateral breast cancer, multiple facial trichelemmomas, acral keratosis, oral papillomas, gastrointestinal polyps, female genital tract tumours and thyroid tumours. The risk of breast cancer in women with Cowden disease is 30-50% by the age 50 years. It does not account for breast cancer outside the families who are affected by the Cowden disease. The gene for it is located on chromosome 10q.

The available data and records till date, suggest that the families with breast cancers differ in their pattern of inheritance and the spread of the disease.

Maurice et al [10], in their study, screened younger women with a family history of breast cancer. Their results strongly suggested that screening young women with a family history of breast cancer led to an improved survival. They also suggested that there should be further follow–up and other “sub-studies” regarding the screening of younger women with a family history of breast cancer to get a precise estimate of the risks and the benefits.

Hampton and Maher [11] studied the pedigree analysis of breast cancer in Oklahoma Indian women. In their study, pedigrees were obtained in five of the nine women who had developed breast cancer between the ages of 25 and 45 years. There appeared to be no correlation between the blood quantum and the age of diagnosis of the breast cancer. It suggested that more pedigree analyses should be done to confirm the hypothesis that breast cancer had occurred in the younger Oklahoma Indian women.

Rajeswari et al [12] studied the risk assessment in the first degree female relatives of breast cancer patients by using the alkaline comet assay. In their study, the comet assay was used to study the basal DNA damage, the DNA susceptibility to a mutagen (N–methyl N-nitro, N-nitrosoguanidine) and the DNA repair efficiency. A significant increase in the DNA damage (baseline and after treatment with a mutagen, as well as after allowing the repairs to take place) and the micronucleus frequency was observed in the controls and their First Degree Family Relatives (FDFRs) and in the FDFRs of the breast cancer patients.

Gajalakshmi et al [13] found a novel BRCA 1 mutation (in a group of 23 Tamil Nadu (south Indian) patients with a positive family history for breast and ovarian cancer). The 1301 de1T is a novel mutation that has not been documented in any population or in any published report to the best of our knowledge. The identification of this novel mutation stresses the need for developing a database of BRCA1 mutations, which will aid in the breast cancer screening in this population.

In the study of Ford et al [14] the contribution of BRCA 1 and BRCA 2 to inherited breast cancer was assessed by linkage and mutation analysis in 237 families , each with at least four cases of breast cancer. It was observed that the lifetime risk of breast cancer appeared to be similar to the risk in the BRCA 1 carriers, but there was some suggestion of a lower risk in the BRCA 2 carriers, at 50 years of age.

Cote et al [15] evaluated the risk of other cancers in individuals with a family history of pancreatic cancer. It was found that a family history of pancreatic cancer was associated with a doubled risk of lymphoma and ovarian cancer among the relatives after adjustment. The relatives with a family history of early – onset pancreatic cancer in a proband had a sevenfold increased risk of lymphoma.

Couch et al [16] noted in their study that in their series, the BRCA 2 mutation accounted for 14% of the male breast cancers, all but one of which had a family history of male and / or female breast cancer.

Armstrong and Davies [17] studied the pedigree of familial breast cancer. In their study report on several relatives who were suffering from breast cancer, the occurrence of neoplasms in 3 generations of a large family was carefully checked for. The members of one out of 8 branches were found to have a high incidence of breast cancer, with 6 women being affected, 4 of them being under the age of 40. They found an early age at onset for bilateral breast cancer, other tumours like ovarian cancer and benign breast disease in the family members.

Teraoka et al [18] found an increased frequency of ATM mutations (miss-sense type) in breast carcinoma patients with an early onset disease and a positive family history.

Fletcher et al [19] suggested that the clinical management of the daughter of a woman with bilateral breast cancer should depend on her CHEK 2 1100de1c carrier status. This and other moderate penetrance breast cancer susceptibility alleles, together with the family history data, will thus identify the increasing numbers of women who are at a potentially very high risk. But it is also important that before such predictions are accepted by clinical geneticists, a further population-based evidence should be obtained on the effect of CHEK 2 1100 de1c and other moderate penetrance alleles in women with a family history of breast cancer.

The Possible Options for High Risk Women

There are 3 methods for the early detection of breast cancer:

Mammography: Mammography i.e. the X-ray of the breast, should be done at regular intervals. But mammography is expensive and technology driven and it requires a stringent quality control and extensive experience on the part of technicians as well as doctors who are involved. If these are not available, mammography can do more harm than good by falsely diagnosing cancer or missing it when it is actually present. In women who are at a higher risk, a mammography surveillance, usually from the age of 35 years onwards, may be advisable. But currently, mammography screening is not advocated for allthe Indian women. Also, some studies have reported that at an earlier age, due to the dense breast tissue, mammography may miss the diagnosis of a breast lump.

Breast Self Examination (BSE): If it is done properly, it is as effective as mammography. The education about this should be initiated in the women in their midteens itself. This involves a description of the natural history of Hereditary Breast Cancer (HBC). At the age of 18 years, they should be taught breast self examination. They should then be told in detail about the pros and cons of genetic testing. The mutation detection test of the "at-risk" women clears the uncertainties and identifies the mutation carriers who are at a high risk for breast cancer.

Genetic testing in India: In women with a significant family history of breast cancer, a specialist surgeon may be needed to be consulted for the statistical assessment of one's individual breast cancer risk.

A pretest genetic counseling is mandatory before a DNA testing. All issues including the implications of a positive test, the implications of a negative test, the limitations of the testing, the options for risk estimation without the genetic testing, the risk of passing a mutation to children, the technical accuracy of the test, the cost of the testing, the risk of psychological distress, the risk of discrimination and the options and the limitations of medical surveillance and screening following the testing should be clearly discussed. The genetic testing should be only done when there is a strong contribution of a hereditary component if it is suggested by the family history. The test should not be done without the availability of adequate pretest and "post-test" counseling.

Cancer surveillance should begin at an early age because there is a high risk for cancer in the younger age groups. Breast cancer surveillance is done by breast self examination (18 years), an annual clinical examination and mammography annually or semiannually, beginning at the age of 25 years.

A prophylactic mastectomy can be offered as mastectomy has been shown to cause a 90% reduction in the incidence of cancer in the mutation carriers and an 80% reduction in the cancer related deaths [20].

The mammographic screening for breast cancer may not be cost-effective in India at present, but regular Breast Self Examination (BSE) needs to be promoted for the early detection of breast cancer. Breast Self Examination can be propagated through print and electronic media, as well as through health care personnel in various settings. The measures which have been identified and propagated for cancer control in the developed countries may not be applicable in the Indian context. We have to find answers to our problems through methods which are feasible and evaluable in the Indian context.

Social issues: While talking about breast cancer, one should also consider the social issues which are related to this. Women who have been diagnosed with breast cancer face a range of issues that differs greatly from those which older and younger women face. Some older women may avoid any kind of treatment because of the fear of the "side-effects" that accompany some therapies, while some may want to take the most aggressive treatment which is available.

Another top issue which some women face is the worry about finances. While already struggling with her health, a woman must then wade into the complicated waters of payments and treatment costs. The problem will become profound and significant if the woman is a widow or if her children are not staying with her and she may lack adequate support.

Stigma: One of the major barriers in the diagnosis and treatment of breast cancer is the social stigma. In Western countries, the stigma is somewhat subtle, but it still exists. But in a country like India, cancer is still considered as a death sentence. Because the general belief is that cancer is untreatable, no matter how much treatment is received and even if the disease has a good prognosis, the society will cast out the cancer sufferers. So, a woman who is diagnosed with breast cancer may beat the cancer and survive, but at what cost? Patients of breast cancer experience great stress during the treatment. The social stigma which is associated with breast cancer and the potential disfigurement of mastectomy pose obstacles in the care of the patients. Thus, even in modern cultures, with the latest technologies and treatments at hand, women and men with breast cancer may feel stigmatized - set apart and marked as too different - leading some of them to feel more victimized by the society than by the disease. Unfortunately, it is the society's loss that breast cancer has got such stigma.

Awareness: As India is rapidly stepping into urbanization, western-ization, resulting in a change in the lifestyle, significantly contributes to the increased burden of breast cancer in the country. A late stage at presentation is the main reason for the poor survival of the cancer patients in India. The late presentation is mainly due to the lack of diagnostic facilities at the peripheral levels and the lack of awareness about breast cancer. So, there is a need to increase the public awareness regarding the prevention, early diagnosis and the treatment which is available for breast cancer. A pink ribbon is the breast cancer awareness symbol. October is the breast cancer awareness month. A public awareness is made by educating the population about the risk factors, and through screening by physical examination or by Breast Self Examination. The strategy which is adopted by the Tata Memorial Centre's Rural Cancer

Project at Barshi in India is aimed at educating the population and at motivating the people to undergo medical investigations. The FBCP (Forum for Breast Cancer Protection) is a non-government organization which is focused on spreading breast cancer awareness. Medical professionals from institutes and hospitals like AIIMS , Sir Ganga Ram Hospital and Rajiv Gandhi Cancer Institute joined together to start FBCP in 2001. So, by making people aware about the details of breast cancer, we can certainly make a positive change in the present picture of breast cancer in India.

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