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Hereditary Breast Cancer: A Systematic Review

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Abstract: **—Breast cancer is a heterogeneous group of tumours with variable prognosis. It is the second leading cause of cancer related death among women.Hereditary breast cancers (HBC) showed around ten percent of the total burden of breast cancer. Most of the breast cancer cases found due to a BRCA germ line mutation. According to estimation, 15–20% breast cancer patients to have one or more 1st or 2nd degree relatives affected with breast cancer. The factors included the genotypic and phenotypic heterogeneity. Many studies found association of HBC with different carcinoma syndromes. The most common association is with ovarian carcinoma so known as hereditary breast ovarian (BO) carcinoma syndrome involving BRCA1 and 2 mutations. Some other factors like reproductive risk factors including age at diagnosis of breast cancer, pregnancy history, and twin history were also studied and were found associated with breast cancer risk. In this review it is reported that knowledge of genetics of hereditary breast cancers may contribute to identification of patient's increased risk of disease. These patients could be subjected to genetic counseling that can be definitely benefited from early diagnosis.**

Keywords: BRCA1, BRCA2, Hereditary breast cancer, reproductive risk factors, genetic counseling

I. Introduction

Heredity is an established risk factor of breast carcinoma. It is used to characterize the women who are at higher risk. The effect of breast cancer risk factors in women with a family history is not very much defined [1]. Hereditary breast cancer accounts for approximately ten percent of total burden of breast cancer. Some studies introduced a well-structured model for breast cancer incidence that included age at menarche, children, history, age at menarche and menopause. According to this model, first child birth was associated with an increase in breast cancer risk, after that a subsequent decrease in risk [1].

Some studies showed the differentiation of breast tissue at the 1stchild birth and lower susceptibility to carcinogens after 1st birth [2, 3]. Reproductive history and other established risk factors may influence the risk of breast cancer differently among women having or not having a family history of breast cancer. In mid 1990s, BRCA mutation testing became available. BRCA permitted an accurate high risk candidate for this disease [4].

The hereditary breast cancer susceptible families were identified by hereditary breast and ovarian cancer (HBOC) syndrome that carried BRCA1and BRCA2 mutations. HBOC syndrome accounted for 30% of all hereditary breast cancer (HBC). So, around 70% of the HBC burden lacks mutations in BRCA1 and 2 [5, 6]. In spite of so much research throughout the world to identify additional mutations involved in HBOC, however the results have remained unclear [7-9].

Walsh et al. 2006 reported the mutation spectra of BRCA1 and BRCA2 which included other high penetrance. Around 12% breast cancer patients with severe family histories of breast cancer found negative for BRCA1 and BRCA2 mutations [6]. Only 5% breast cancer cases carried a large genomic deletion or duplication in BRCA1 or 2 genes, or in other genes (CHEK 2 OR TP53) [6].

II. Levels of the pedigree group

Almost all studies classified the patients into three pedigree groups (Figure 1).The genetic relationship among the original patient known as1º proband and other relative affected with breast cancer were known as 2º pro band was basis for defining three pedigree groups. In those pedigrees where mother of the patient was the 2ºproband called as the mother pedigree group. On the other hand where a sister was 2ºproband called the sister pedigree group. Remained groups considered as second degree group [10-12].

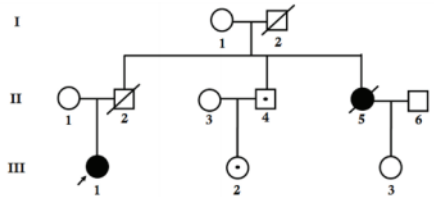

Figure 1: Pedigree structure of the hereditary breast carcinoma. Solidus; Diseased. Roman numerals; generations (I-III). Proband; shading and arrow. Squares and circles; males and females, respectively. Carriers; dot within the square or circle.

Some studies reported that 1stdegree relatives were characterized by high breast cancer risks; whereas the sister and second degree pedigree groups are characterized by lower breast carcinoma risk [13, 14].The genetic effect would be expected to be minimum in the 2nddegreepedigree group. The mother pedigree group included such a hereditary form of breast cancer, where three generations affected with breast cancer that means that daughters of patients have about 27-32% possibility of breast cancer development.

The hereditary breast cancers are site-specific disease [13]. These can be identified by the familial occurrences of associated carcinoma, like familial occurrence of early breast carcinoma related with soft tissue sarcomas or the familial association of breast carcinoma and colon carcinoma [15, 16]. In an earlier study, other hereditary types around 10% of the pedigrees were identified. However, they were not confined to any pedigree group and their removal had no important hereditary effect on the risks [17, 18].

III. Age at diagnosis

Among familial breast cancer patients, the younger age at diagnosis of breast cancer was observed in breast cancer patients as compare to the others [13, 14, 19, 20]. Early age in the familial patients is consistent with the results of a 2step mutation

model proposed by the scientist Knudson. This model predicted the patients with hereditary basis for disease will have an earlier age at onset than the patients with a non hereditary basis. Some studies supported this model and indicated first degree relatives were identified by high breast carcinoma risks; on the other hand sister and 2nddegree relative's pedigree groups were identified by lower carcinoma risks [14].

IV. Risk factors associated with reproductive history

In some studies, it was reported that there is a constant increase in the risk of breast carcinoma in a mother or sister with family history of breast cancer that was related by 1stpregnancy [1]. Many studies found that parous women were at higher risk of breast carcinoma than the nulliparous women [1, 17, 21].

Women having no family history of breast cancer, 1st child birth were associated with high risk of breast cancer. Early pregnancy and high number of children were related with decreased breast cancer risk. However, the bad effect of early menarche was decreased in women having family history of breast cancer. In postmenopausal women with family history of breast cancer, the bad effect of pregnancy persisted up to 70 years of age [22].

IV.1 Twins history

Floderus et al. (1990) compared family history of breast cancer by the twin babies with carcinoma [23]. They observed a 50% of family history of breast cancer affected twins. The authors hypothesized that it was a conservative estimate, as twin babies could be in closer contact than siblings in general. Results from the Iowa women's health study showed a lower relative risk for a family history of breast cancer in a first-degree relative. Sometimes it is associated with the old age of that particular population [24].

IV.2 Age at menarche

The effect of later age at menarche was taper off in women with a family history of breast cancer [25]. The finding was consistent with several other studies of risk factors among women with or without a family history of breast cancer [26, 27]. Data of the Iowa Women's Study indicated reproductive factors were related differently with breast carcinoma risk related to family history.

Later age at menarche showed a protective effect that is limited to women without a family history of breast cancer. Number of live child births was not found related to breast cancer risk among women without a family history. Analysis was based on classification according to age at first child birth or parity [24].

IV.3 Pregnancy history

Some studies reported that pregnancy after exposure to carcinogens increases the rate of tumor growth as compared to pregnancy before exposure [28]. Some studies found this term was statically significant only for 1stfull term pregnancy and not for subsequent pregnancies. This hypothesis suggested that breast is expected to be protected against effects of cell proliferation during second & subsequent pregnancies [17].

Increase in breast cancer risk was found related with 1stfull term pregnancy which was followed by a decrease rate of risk in the rate of cell turnover. It also account for the interaction between age and age at first birth and breast cancer risk [29]. The studied incidence data from New York State showed that a crossover in breast cancer incidence between married & un married women at the age of 42 years. They observed that married women showed higher incidence than unmarried women before this age and lower incidence after this.

A similar crossover of incidence has been reported in black and white women which was constant with the distribution of age at first birth by race [30, 31]. Over many decades, black women in the US had increased rates of pregnancy as well as early age at first child birth as compare with white women of US [32].

V. Genetic modification in hereditary breast cancer

Modification of genetic in breast cancer risk is characterized by the increased incidence of breast carcinoma in women with a family history. Linkage analysis studies of families have showed the high penetration of genes being the probable reason of inherited breast carcinoma risk in families [33].

Alterations in genes are quite rare, and account for around ten percent of breast carcinoma patients. It is possible that important background genetic factors may contribute to the etiology of breast cancers [34]. Autosomal dominant inherited disposition to breast cancer is identified by early age at onset of breast carcinoma i.e. transfer through both mother and father. Three principal syndromes found associated with breast cancer risk i. e.:

(i) Due to BRCA1 or BRCA2 mutations

(ii) Li Fraumeni syndrome due to mutations in the p53 and hCHK2 gene.

(iii) Cowden syndrome due to PTEN mutations [35-37].

Mutations in these genes give different phenotypes of particular carcinoma. Other syndromes, that included breast carcinoma, may be ataxia telangiectasia and Peutz Jeghers syndrome. Ataxia telangiectasia is primarily an autosomal recessive disorder. It is hypothesized that around 1one percent of the general population may be heterozygous carriers of ATM gene [38]. Over two hundred mutations have been identified in these genes till date. Maximum of those are truncated mutations [39]. Many epidemiological studies have suggested a significant increased breast cancer risk among heterozygous carriers. The estimated relative risk studied ranged from 3.9 to 6.4 [40]. Peutz-Jeghers syndrome is an autosomal dominant disorder(early onset) [41]. Germline mutations in S.T.K.1.1 found responsible for fifty percent of Peutz Jeghers syndrome [42]. Patients having this syndrome hadaincreased breast cancerrisk [43].

VI. BRCA1 &2 genes

BRCA1 gene is present on chromosome no. 17q21.It contains twenty four exons encoding a protein of 220 kDa. It is made up of 1863 amino acids (Figure 2) [33, 44]. The second breast cancer causing gene i.e., BRCA2, is present on long arm of chromosome no. 13. BRCA2 is a large gene, composed of twenty seven exons encoding a protein of 380 kDa [45]. Both these genes are nonhomologous.BRCA1 &2 have a large exon no.11 and translational start site in exon no. 2. Their proteins are normally located in the nucleus and containing phosphorylated

residues [44, 45]. BRCA1 gene contains two protein motifs and ring finger domain along with the BRCT domain near C terminus. These domains may facilitate both PPI and PD interactions. The BRCT domain is a phylogenetic conserved sequence present in the proteins which are involved in DNA repair as well as regulation of cell cycle [46].

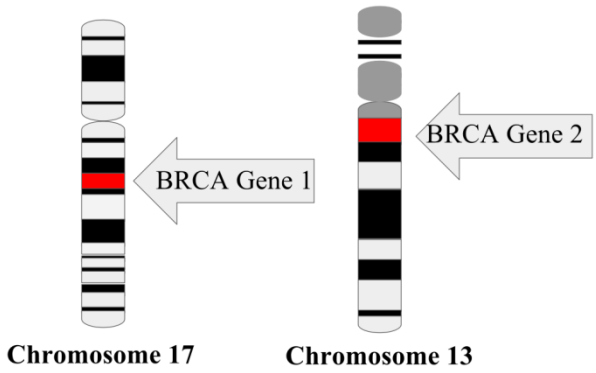

Figure 2: Breast cancer causing genes BRCA2 & BRCA 2 location on human chromosomes

BRCA2 has no protein motifs and no direct relationship with other breast cancer causing gene BRCA1. Although BRCA1 and BRCA2 share many functional similarities which suggest that how mutations in both of these genes have a specific hereditary disposition to breast cancer. However, accurate molecular function of both of these genes and their mutations inducing breast carcinoma remain unclear till now. However, it is also observed that BRCA proteins are involved in many cellular functions, like integrity of genome, cell growth as well as cell differentiation [47, 48].

Evidences suggested that BRCA1 &2 is directly involved in the DNA repair process, gene expression regulation & embryogenesis [47, 49, 50]. The end products of both of these genes i.e. proteins, get interacted with different other proteins which are associated with homologous chromosome recombination and double stranded break repair mechanisms [50]. These results are important for finding mechanisms of BRCA tumor formation, as well as suggesting a genotype based method for choosing different treatment strategies for breast carcinoma in women with BRCA mutations [51].

VII. Allelic variants of BRCA1 & BRCA2genes

BRCA1 and 2 genes acts as tumor suppressor genes, when there is loss of the unaltered allele of genes [52, 53]. Women with mutation in one of the two genes i.e. BRCA1 & 2. The allele has a high risk of breast cancer development [54]. The pathology of BRCA gene allelic variants can lead to differential function of the proteins, DNA repair or transcriptional activity. Accumulation of the side effects could results in chromosomal instability which may cause carcinoma formation.

Mutations in BRCA1 & 2, give a highly increased susceptibility to breast cancers. The current scenario is that these are also known as caretaker genes. Upon removal of these genes other genetic disorders may accumulate. Nature of these biological events can define the path by which BRCA1 & 2 function. Nearly two thousand different sequence variants in BRCA1 &2 have already been reported. The mutation pattern is very complicated and heterogeneous.

In both of these genes, alterations are distributed uniformly along with the entire exonic as well as intronic sequences flanking the exons. The alterations which are associated with high breast cancer risk results in complete protein miss or non functional proteins. This supports the hypothesis that BRCA1 & 2 is tumor suppressor genes.

It is suggested that BRCA1 & 2 mutations showed different expression w.r.t. breast, ovarian and other related cancers. A study on one hundred and six families was screened for BRCA1 & 2 point mutations and small deletions. Analysis of mutation was performed by the automatic direct sequencing technique. The total of different forty six families was found carriers for BRCA1&2 mutations. No mutations were found in 57% of families. Different other variants of uncertain molecular significance were also found.

VIII. Frequency distribution of pathological allelic variants i.e. founder mutations

The maximum number of BRCA alterations has been reported in many families. A small number of such mutations have been found in many families in the same ethnic group this is known as founder effects. Approximately one out of eight hundred women in general population may carry alterations in BRCA1. The percent frequency of BRCA1 mutation carriers has been reported in selected groups of families [55, 56].

The examples of founder mutations had been described in some studies [58]. In this study the carrier percent frequencies for these mutations was determined in some studies [57]. Overall, the percentage frequency of such mutations is one in fifty Ashkenazi Jews. Around twenty five percent of early-onset breast carcinoma and has been found in 90% of families [58].The founder mutations were found in Netherlands (BRCA1), Iceland (BRCA2) and Sweden (BRCA1) [59, 60].

Founder mutations have also been found in some areas of some restricted areas of Italy. A founder effect was identified in a country (Italy) for both BRCA1 & 2 [61, 62]. A new founder mutation was described in Tuscany. In this study, 1^0 haplotype analysis of eleven families was detected (1499 ins) in BRCA1 gene. A haplotype was found with a high frequency associated with these mutations in the general population [63]. The presence of such founder mutations had direct application in genetic testing.

IX. Pathology and allelic variants of breast cancer

The phenotype for BRCA related tumors appeared to be heterogeneous, and is better described in BRCA1 as compared to BRCA2 [64]. The pathological features of breast cancer in women with BRCA1, mutations showed a number of high grade tumors, lack of in situ ductal carcinoma, high mitotic rates, high rate of aneuploidy, lacking estrogen receptor-negative and high frequency of great intensity immunostaining of p53 [65].

X. Genetic Counseling

The genetic counseling is an important part of any cancer genetic testing study. This is basically a management program, taking place before exact analysis of FNAC or pathogenetic studies. The consent should be obtained from patients so that protection of confidentiality will ‘secure according to the regulations of the health insurance, portability & accountability

act [66]. Patients should be fully informed about the different faceted issues related with genetic testing. In case of hereditary breast ovarian cancer (HBOC) syndrome, the patient must be fully apprised of the fact that failure to identify a BRCA1 or 2mutation in the family does not exclude the presence of hereditary factors [4]. The remainder of HBOC cases would be due to identified alterations [6]. The high risk patients must also be appreciated the fact that BRCA mutations are not exactly penetrant.

XI. Conclusion

This review covered the knowledge of reproductive factors and human genetics facts which are important for the diagnosis and analysis of most forms of hereditary breast carcinoma, particularly the hereditary breast cancer syndromes. A large number of studies have pointed out the role of heredity, reproductive risk factors, genetic contributions in different genes like BRCA1 & 2related with breast cancer risk. However, due to limited knowledge on family history in the etiological studies of breast cancer, its role is not fully understood. There is need of best expertise physician who examine the patients carefully and recommend regular clinical breast cancer examination and mammography for all women over the age of 50 years, for both those with and without a family history of breast cancer.

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