Review Article

ROLE OF MODERATE RISK SUSEPTIBILTY GENES IN DEVELOPMENT OF BREAST CANCER

ABSTRACT:

Breast cancer is the most common cause of mortality in females globally and affects the lives of millions of women. It is a leading cause of mortality worldwide, but the dynamics have been changed due to advanced screening and treatment protocols (1). In the United States, breast cancer has been ranked second most common cause of cancer-related death in women with the most common being lung cancer (2). To improve cancer screening a personalized approach has been discussed but its implication over large populations can be difficult and requires expertise. Early detection leads to good prognosis whereas late diagnosis of breast cancer is a challenge for both patient and doctor.). Breast cancer became the most prevalently diagnosed cancer worldwide as of 2021 accounting for 12% of new annual cases worldwide, according to the World Health Organization. In2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. Multigene panel testing has identified various genes predisposed to breast cancer development. All of these genes have different penetrance abilities. BERCA1 and BERCA2 gene are best known high penetrance gene of hereditary breast cancer . Their discovery has revolutionerized effect in the field of cancer assessment. Tumors from BERCA1 and BERCA2 shows distinctive clinicopathological characteristics as compared to other genes causing tumors. Beyond BERCA1 and BERCA2, advances in molecular technique have led to the identification of other genes associated with breast cancer. Some other high penetrance genes are TP53, PTEN, STK11, and CDH1. Besides high pentrance gene, moderate to low penetrance genes also recognized as a cancer predisposing gene: PALB, BRIP1, ATM, CHEK2, BARD1, NBN, NF1, RAD51C, RAD51D . Along with risk of breast cancer development these genes also predispose to other malignancies, as well as some genetic disorders.

Comment [A1]: REFERENCE IS MISSING

INTRODUCTION

Breast cancer is the most common cause of mortality in females globally and affects the lives of millions of women. It is leading cause of mortality worldwide, but the dynamics have been changed due to advanced screening and treatment protocols (1). In the United States breast cancer has been ranked second most common cause of cancer related death in women with the most common being lung cancer (2). To improve cancer screening a personalized approach has been discussed but its implication over large populations can be difficult and requires expertise. Early detection leads to good prognosis whereas late diagnosis of breast cancer is a challenge for both patient and doctor (3). The incidence of breast cancer and mortality rate is highest in women after menopause and is also affected by racial disparities (4). Breast cancer became the most prevalently diagnosed cancer worldwide as of 2021 accounting for 12% of new annual cases worldwide, according to the World Health Organization. In the U.S every 1 in 8 women develop invasive breast cancer in her lifetime (5).In2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. There are more lost disability-adjusted life years (DALYs) by women to breast cancer globally than any other type of cancer (6). Breast cancer is more prevalent in Black women than in white women under 45. Black women are more at risk of dying from breast cancer. The risk is lower in Asian, Hispanic, and Native American women. Ashkenazi women have a higher rate of BERCA mutation therefore higher risk of breast cancer (5). It is a leading cause of cancer-related death in women globally. Worldwide it is accounted for 684,996 deaths [95% UI,675,493-694,633] at an age-adjusted rate of13.6/100,000. Although prevalence rates were highest in developed regions, the countries in Asia, Africa shared 63%of total deaths in 2020(7). Counties with low to medium income are expected to have an increased incidence of breast cancer due to lifestyle westernization (e.g., delayed pregnancies, reduced breastfeeding, low age at menarche, reduced physical activity, and poor diet), early cancer detection and registration (8). Several procedures have been implemented to reduce the incidence and mortality rate of breast cancer includes general preventive measures and screening programs for early detection of cancer and treatment and for this Breast Health Global Initiative (BHGI) is making proper guidelines and approaches (9).

According to World Health Organization, Breast cancer occurs from the cell lining (epithelium) of the ducts (85%) or lobules (15%) in the glandular tissue of the breast. When it is confined within the lobules or ducts it is in-situ and when spread beyond it is metastasis (6). Many risk factors have been recognized including both modifiable and non-modifiable risk factors. Table.1(4)

Table No.1
Modifiable And Non-Modifiable Risk Factors

Non-Modifiable Factors	Modifiable Factors
Female sex	Hormone replacement therapy
Older age	Diethylstilbestrol
Family history (of breast or ovarian	Physical activity
Genetic mutations	Overweight obesity
Race/ethnicity	Alcohol intake
Pregnancy and breastfeeding	Smoking
Menstrual period and menopause	Insufficient vitamin supplementation
Density of breast tissue	Excessive exposure to artificial light
Previous history of breast cancer	Intake of processed food

Non-cancerous breast diseases	Exposure to chemicals

World Health Organization has classified at least 18 different histological types of breast cancer (10). Invasive Breast cancer is categorized into two main groups Invasive breast cancer of no special type previously known as Invasive ductal carcinoma accounting for 40-80% (11). About 25% of invasive breast cancer shows distinguish growth pattern and cytological appearance hence known as specific subtypes [e.g., invasive lobular carcinoma, tubular, mucinous A, mucinous B, neuroendocrine] (12). Molecular classification is independent of histological subtypes, based on mRNA gene expression four molecular subtypes have been identified [Luminal, HER-2 enriched, Basal-like, and Normal breast-like] (13). Luminal is further divided into luminal A and Luminal B, both A and B subtype and HER-2 enriched comes under the category of non-basal invasive breast cancer. Basal-like breast cancer (TNBC) is previously also called triple-negative due to the absence of estrogen receptor (ER−), progesterone receptor (PR-), and human growth factor neu receptor (Her2) responsible for about 10% of all breast cancer (14).

GENETIC RISK FACTORS FOR DEVELOPMENT OF BREAST CANCER

There are various factors increasing the development of breast cancer and having protective effects towards breast cancer. Factors decreasing the chances of breast cancer include pregnancy in early age, high parity, breast feeding, healthy diet, daily physical activity,and use of chemo preventive agents. Genetic polymorphisms account for sensitivity of environmental carcinogens and their impact on cancer genes. Single nucleotide polymorphisms with double strand DNA breaks and caspase 8 gene are found to be associated with breast cancer risk (15). A positive family history for breast cancer is the most important risk factor and almost 20% cancer

patients have affected first degree relatives. In females with family history, the cancer usually occurs bilaterally and in early age with autosomal inheritance (16).

GENES RELATED TO BREAST CANCER

- **BRCA1:**

The discovery of BERCA1 gene was a great development in explicating the genetic aetiology of breast cancer. The inactivating mutation of BERCA protein raises the risk of development of breast, ovarian, and other cancer. It is high penetrance autosomal dominant gene for breast cancer. Germline mutation of BERCA1 and BERCA2 accounts for 25% risk of familial breast cancer (17,18,19), and therefore 5-10% overall risk for all breast cancer (20). BERCA1 is located on chromosome17 long arm (21). Main functions of BERCA1 include cellular regulation, DNA damage control, cell cycle control, transcription process control, and ubiquitination (21). These functions contribute to its tumor suppressive abilities. BERCA1 mutation accounts for 40-45% of hereditary breast cancer. In about 80% of families with increase incidence of breast and ovarian cancer BERCA1 mutation is mainly responsible. However BERCA1 expression is increasingly reduced in sporadic cancer (22). Estrogen receptor marker is usually absent in 90% of patients having BERCA1 mutation (23). BERCA1 mutation carriers are also deficient in expressing PR cells as well as reduced number of HER2 expressing cells(24). BERCA1 related tumors are similar in genotype, phenotype, and clinical expression to sporadic basal-like tumors(Triple Negative Breast Cnacer[TNBC] (24). Basal-like tumors have defective BERCA1 pathways. More than 60% promoter gene underwent methylation resulting in downregulation of BERCA1(25).

- **BERCA2:**

Tumor suppressor BERCA2 gene(MIM6oo185) is a high penetrance autosomal dominant gene. An approximated cumulative risk of breast cancer is 27-84% for BERCA2 carriers at 70 years of age and corresponding ovarian cancer risks are 11-30%(26). Many detrimental mutations are small deletion or insertion during transcription that results in truncated protein translation. The frequency of these mutations differs in different populations particularly in fonder populations(16). BERCA2 is located is on chromosome 13 and encoded a larger protein than BERCA1. Its tumor suppressing roles are instrumental in repair of double stranded DNA break, genomic instability regulation, cell cycle regulation, cell growth, apoptosis, and chromosomal remodeling(27). BERCA2 is an estrogen positive variant with similar expression of PR cells but lower frequency of HER2 cells(24). The estimated prevalence of BERCA1/2 in general populations are 1:400 to 1:500 of people(28), BERCA2-related tumor tends to be less distinctive than BERCA1-related tumor with higher grading, high mitotic index, and less distinctive tubule formation(16). Bi-allelic form of germline mutation of BERCA2 has an association with subgroup of fanconi anemia that raises the susceptibility of childhood tumor(29). The therapeutic applications of BERCA1/2 include assessment of cancer risk, prognosis, and therapeutic intervention required(30).

- **CHEK2:**

Cell cycle checkpoint kinase 2 gene(CHEK2 or CHK2) has beeb identified as a intermediate penetrance breast cancer risk gene due to its involvemrnts in DNA repair mechanism and replication regulation(31,32). The product of this gene works as serine/threonine protein kinase that phosphorylates BERCA1, p53, and Cdc25 family proteins(33). Three germline mutation has been identified in different studies: 1100delC, R145W, I157T and distinguishingly recognized to be associated with breast cancer(34,35). The 1100delC mutation is the most extensively studied and it results from deletion of single cytosine at 1100 position on gene that causes lack of kinase function of protein(36). The other common variants I157T has substitution mutation of isoleusine to threonine and missence mutation in R145W producing truncating protein product that lost its ability to bind with BERCA1, p53, and Cdc25 family(33). Prevalence of CHEK2 mutation especially 1100delC mutation is vary in different population.

The prevalence is in Finland(6.8%) followed by Netherland(4.9%) , in U.K and Germany it is 1.2% and 0.8% respectively(37).

- **P53:**

Tumor protein 53(TP53) is a tumor suppressor gene responsible for decoding p53 phosphoprotein(38). It is located on chromosome 17p13.1. it plays a crucial role in regulation of gene, apoptosis, DNA repair, and cell cycle arrest(39). Basal-like tumors have high risk of somatic mutation in TP53(40) although TNBC is not associated with increased risk of TP53. In a cohort of 2,134 BERCA1/BERCA2 negative women with familial breast cancer the mutation rate of TP53 was 0.52% and carriers was HER2 positive(41). Li-Fraumeni Syndrome(LFS) is associated with TP53 mutation and lifetime risk of breast cancer in LFS is 25-79%(42).

- **PTEN:**

Phosphatase and tensin homolog(PTEN) is another most frequently mutated human gene after PT53. It is involved in the regulation of phosphoinositol-3-kinase and AKT signaling pathways(43). Germline mutation in PTEN is also found in Cowden Syndrome which has life time risk of breast cancer of about 50%(44). According to NCCN guidelines, screening of women with PTEN mutation should start at 25 years of age with breast examination, yearly mammography, breast MRI screening with contrast at 30-35 years of ag(45). Most PTEN associated tumor are luminal in nature than TNBC(46).

- **PALB2:**

PALB2 is a localizer and stabilizer of BERCA2 gene it binds with BERCA2 protein and regulates its nuclear structures such as chromatin, nuclear matrix and also recombinational repair and checkpoints functions promator. Its gene located on chromosome 16p12.2(47). It is now ranked as a high risk breast cancer gene accounting for odd ratio(OR) of 7.46(48). It shows aggressive disease progression. Finland reported more than 50% women with PALB2 mutation presented with TNBC(49). PALB2 gene is also associated with Fanconi anemia in its biallelic form. However monoallelic form of PALB2 gene accounts higher risk of breast cancer for both

sexes(50), estimated of about 53% for female and 1% for male by the age of 80(51). Risk of ovarian cancer(52) and pancreatic cancer(53) has also low increased in PALB2 gene mutation accounting for 5% anf 2-3% respectively(51).

- **STK11:**

Serine/threonine protein kinase11(previously LKB1) is a high penetrant gene for breast cancer(54). It is present on chromosome 19p13.3 and encodes serine and threonine and its main functions are regulation of energy metabolism and cellm polarity(55). Peutz-jehgers syndrome was found to be caused by germline mutation in STK11 gene(56). It is an autosomal dominant disorder with features of melanocytic macules of the lips, buccal mucosa and digits, multiple gastrointestinal hamartomatous polyps, and increased risk of various cancers.patients with STK11 carriers having lifetime risk of breast cancer is 32-54% and other gynaecological tumors(cervical,ovarian,uterine) is 13% by the age of 60(57). According to NCCN guidelines, the screening starts at the age of 25 and it includes clinical examination of breast 6 monthly ,yearly mammography, and breast MRI(58).

- **CDH1:**

The Cadherin 1 (CDH1) gene encodes an adhesion molecules and has main function is to maintain cell morphology(44) through it prevents invasiveness and metastatization(59) and also acting as tumor suppressor(60). Hereditary diffuse gastric cancer syndrome(HDGC) is associated with germline mutation in CDH1(61). It is an autosomal dominant disorder characterized by diffuse-type gastric cancer(DGC) and lobular type breast cancer(LBC). The women having cumulative risk of lobular breast cancer with germline mutation of CDH1 accounting of 39-52% by 80 years of age(62). It is unlikely that CDH1 germline mutation has an association with TNBC because most of the CDH1 mutated lobular breast cancer are ER positive. Accordingly, germline mutation of CDH1 in women with TNBC were very rare of about 0.0-0.3%(46).

- **ATM:**

The ataxia telangiectasia mutated (ATM) gene is present on chromosome 11q22.3 and encodes phosphatidylinositol-3-kinase protein. It ia also acts a tumor suppressor gene and and involve in repair of DNA damage by phosphorylation process and cell cycle control(63). Ataxia telangiectasia is associated with biallelic form of ATM germline mutated gene. It is an autosomal recessive disorder containing features are cerebellar ataxia, telangiectases, immune defect, and various predisposition to malignancy(64). On the other hand monoallelic form of ATM mutated gene is associated with cumulative risk of breast cancer accounts for 17-52% during lifetime(65). According to NCCN guidelines, screening shoul start at the age of 40 in women with an ATM mutated gene, it includes annual mammography with consideration of tomosynthesis, breast MRI with contrast(45). Studies have observed that ATM mutated tumors are enriched with ER positive tumors(41). The risks have been increased to five folds in patients with non TNBC tumors for ATM mutation in comparison to TNBC tumors(46).

- **RAD51:**

The RAD51 gene encodes a protein that is responsible for the repair of double stranded DNA break. In mammals, seven RAD51 paralog has been recognized: RAD51, RAD51B,RAD51D, XRCC2, XRCC3, and DMC1(66). Biallelic form of RAD51, RAD51C, and XRCC2 are associated with Fanconi anemia(67). On contrary, monoallelic form of RAD51 and its paralog has malignant predisposition, specifically RAD51B, RAD51C, and RAD51D has ovarian cancer risk and RAD51D, RAD51B, and XCCR2 has breast cancer risk(68,69). Greater than three fols increased risk has been associated with RAD51D mutation. Mutation rate ranges from 0.20 to 0.95% in patients with TNBC in comparison to non-TNBC, in them rates are lower(0.5%)(46). According to NCCN guidelines, screening should start at the age of 45-50 or earlier based on family history(45).

CONCLUSION:

Breast cancer comes under the category of top 10 most common and most deathly tumor for women and genetic predisposition plays a crucial role among risk factors for cancer development. Discovery of BERCA1 and BERCA2 has been done decades ago as a high pentrance predisposing gene for breast cancer. Accurate estimation of cancer risk assessment , as

well as surveillance protocols for early detection and prevention are available(70,71). New NCCN guideline stated that genetic testing can be done in a patient diagnose with TNBC at ≤60 years with or without significant family history of breast cancer(72). Screening programe that has been set, should be prioritized because it has a critical importance in decreasing the mortality rate of breast cancer. The impotance to identify genetic etiology extends beyond risk assessment as it is also helpful in management strategy and therapy selection.

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