Review

Breast cancer genetic susceptibility: With focus in Saudi Arabia

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A R T I C L E  I N F O

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A B S T R A C T

In recent years there have been important advances in molecular genetics and linkage analysis of the breast cancer. Beside germline BRCA1 or BRAC2 mutations, and somatic genetic alterations, epigenetic alterations in numerous genes play an essential role in the tumorigenesis of breast cancer. TP53, STK11, PTEN, CDH1, NF1 or NBN mutations are associated with high breast cancer associated syndromes. Mutations in DNA repair associated genes (ATM, CHEK2, BRIP1, PALB2 and RAD50) are associated with increased breast cancer risk. Moreover, several single nucleotide polymorphisms (SNPs) were considered as breast cancer susceptibility polymorphisms within genes (FGFR2, TOX3, LSP1, MAP3K1, and TGFBI). This review discusses breast cancer genetic susceptibility, highlights recent advances in breast cancer genetics, with a particular focus in Saudi women.

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1. Introduction

Cancer is the 2nd leading cause of death worldwide. Up-to-date estimates on cancer burden require an urgent need for cancer control planning. Breast cancer is the most frequent females’ cancer with 2.4 million cases. This cancer was also the leading cause of cancer deaths and disability for women with 523,000 deaths and 15.1 million years lived with disability (YLDs). Breast cancer characterized by its molecular and clinical heterogeneity. Genic profiling studies have categorized breast cancers into five subtypes: luminal A, luminal B, HER-2 overexpressing, basal-like, and normal breast-like. Although clinical dissimilarities between subtypes have been well defined in the literature, etiologic heterogeneity have not been fully deliberated. Breast cancer influenced hormonal factors such as age, parity, age at first full term birth, breast feeding and hormone replacement therapy has strong relation with luminal breast cancer subtype. Hormone replacement therapy is usually associated with the risk of breast cancer overexpressing HER2. Triple negative breast cancer subtype is commonly in obese, particularly premenopausal women.

A hereditary predisposition to breast cancer chiefly affects screening and follow-up endorsements for women at high-risk. But, in patients with a suggestive personal and/or family history, a specific predisposing gene is identified in <30% of cases. Up to 25% of hereditary cases are caused by a mutation in one of the few demonstrated uncommon, but highly penetrant genes (BRCA1, BRCA2, PTEN, TP53, CDH1, and STK11), which award up to an 80% lifetime risk of breast cancer. An extra 2%–3% of cases are related to a mutation in an infrequent, moderate-penetrance gene (e.g. CHEK2, BRIP1, ATM, and PALB2), each linked to a twofold upsurge in risk. Prediction models propose that there are improbable to be extra yet to be identified high-penetration genes. Analysis of common, low-penetrance alleles contributing to risk in a polygenic mode has generated a small number of indicative single-nucleotide polymorphisms (SNPs), but the contributive risk of an individual SNP is fairly minor. Mutation analysis is presently suggested for individual genes in the suitable clinical design where there is a high index of suspicion for a specific mutated gene or syndrome. Subsequent generation sequencing offers a new setting for risk estimation. Currently, there are distinct clinical guidelines for individuals with a mutation in a high-penetrance gene. Otherwise, standard models are used to guess an individual’s life time risk by clinical and family history rather than genomic information.

Numerous studies have described that breast cancer risk factors seem to be related to the interaction between certain genes and exposure to various environmental factors. Breast cancer is the most common cause of cancer-related deaths among Saudi women. In 2012, BC accounted for 25.8% of all newly diagnosed cancers in the female Saudi population. This review discusses breast cancer genetic susceptibility, highlights recent advances in breast cancer...
genetics, as well as, considers publications pertaining to this issue from Saudi Arabia.

1.1. Germline mutations in BRCA1 or BRCA2

Hereditary breast cancer regularly results from disturbance of the normal functions of BRCA1 and BRCA2. Germline mutations in BRCA1 or BRCA2 deliberate an increased lifetime risk of developing breast cancer, but inconstant penetrance proposes that cancer susceptibility is susceptible in part by modifier genes. Germline BRCA1 or BRCA2 mutations, which account for 20–40% of breast cancer that clusters in with an average lifetime risk of 8–10%. Up to 15% of healthy women have no less than one first degree relative with BRCA1 and observed data display that breast cancer risk doubles in such women. It is assumed that monogenic traits account for 5% of breast cancer overall. Mutation in BRCA1 or BRCA2, which gatherings in families and less than 5% of breast cancer inclusive, are accompanying with a high lifetime risk of up to 60–85% for breast cancer as well as a greater risk for ovarian cancer. In addition to this high risk in hereditary breast cancer, there are definite heritable syndromes related to an amplified breast cancer risk. However, more than 50% of the genetic susceptibility to familial breast cancer remains unexplained.

BRCA1 was the first major gene associated with hereditary breast cancer, which is located on chromosome 17. BRCA1 gene was discovered in 1990 using linkage analysis in families with suggestive pedigrees. In 1994, BRCA2 was mapped to chromosome 13. A mutation in either BRCA1 or BRCA2 deliberates an augmented breast cancer risk. Massive relocations and deletions in BRCA1 or BRCA2 can also change the function of BRCA, causing an identical clinical syndrome to that seen in carriers of mutations in BRCA genes. The clinical syndrome seen in BRCA mutation carriers is referred to as the Hereditary Breast/Ovarian Cancer (HBOC) syndrome, though there are patients with this same clinical picture who are found to be negative for mutations in both BRCA1 and BRCA2. Tumors resulting from mutations in BRCA1 tend to be of the basal-like phenotype, have a high histologic grade, and do not commonly express the estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor 2 (HER2), the so-called triple-negative tumor. BRCA2-related tumors more closely look like sporadic tumors.

Although, BRCA1 and BRCA2 mutations are inherited in an autosomal dominant fashion, but behave recessively on the cellular level as tumor suppressor genes involved in double-stranded DNA (dsDNA) break repair. It was well established that BRCA1 or BRCA2 mutations’ female carriers have a lifetime risk of 50%–85% to develop breast cancer. Male carriers of BRCA1 have an increased breast cancer risk, nonetheless to a minor degree than carriers of BRCA2 who have an expected 5%–10% lifetime risk.

A recent study have shown that, the cumulative breast cancer risk to age 80 years was 72% (95% CI, 65%–79%) for BRCA1 and 69% (95% CI, 61%–77%) for BRCA2 carriers. Breast cancer incidences increased rapidly in early adulthood until ages 30–40 years for BRCA1 and until ages 40–50 years for BRCA2 carriers, then remained at a similar, constant incidence (20–30 per 1000 person-years) until age 80 years. The cumulative ovarian cancer risk to age 80 years was 44% (95% CI, 36%–53%) for BRCA1 and 17% (95% CI, 11%–25%) for BRCA2 carriers. For contralateral breast cancer, the cumulative risk 20 years after breast cancer diagnosis was 40% (95% CI, 35%–45%) for BRCA1 and 26% (95% CI, 20%–33%) for BRCA2 carriers (hazard ratio [HR] for comparing BRCA2 vs BRCA1, 0.62; 95% CI, 0.47–0.82; P = .001 for difference). Breast cancer risk increased with increasing number of first- and second-degree relatives diagnosed as having breast cancer for both BRCA1 (HR for ≥2 vs 0 affected relatives, 1.99; 95% CI, 1.41–2.82; P < .001 for trend) and BRCA2 carriers (HR, 1.91; 95% CI, 1.08–3.37; P = .02 for trend). Breast cancer risk was higher if mutations were located outside vs within the regions bounded by positions c.2282–c.4071 in BRCA1 (HR, 1.46; 95% CI, 1.11–1.93; P = .007) and c.2831–c.6401 in BRCA2 (HR, 1.93; 95% CI, 1.36–2.74; P < .001).

In Saudi Arabia, genetic germline testing, usually performed in a blood sample on basis of family history, applying whole-exome sequencing or a massively parallel sequencing technology and verified by Sanger sequencing. However, the results of genetic germline screening still has limited utility in Saudi Arabia. It is only utilized at personalized levels. Therefore, the a need for further efforts in this context in Saudi Arabia.

In Study from Saudi Arabia performed whole-exome sequencing of seven breast cancer patients with positive family history of the disease using the Agilent SureSelect™ Whole-Exome Enrichment kit and sequencing on the SOLID™ platform. The study identified several coding single nucleotide variations that were either novel or rare affecting genes controlling DNA repair in the BRCA1/2 pathway. The study concluded that, the disruption of DNA repair pathways is very likely to contribute to breast cancer susceptibility in the Saudi population. However, a recent study from Saudi Arabia, reported that the overall frequencies of the BRCA germline mutation was 10.2%.

ER, PR and HER2: The genetic profiling of breast cancer is important step toward classification of breast carcinomas, treatment choice, predicting of response to treatment, and indication of risk of recurrent. ER, HER2 receptors are the most important genes in genetic profiling and in determination of adjuvant type. These biomarkers are routinely tested for all breast carcinomas.

ER, HER2 receptors, and proliferation-related genes are the leading drivers of classification in many of the gene expression profiling tests for breast cancer. However, ER, PR) and HER2 receptor status remain crucial in defining the requirement and type of adjuvant therapy. These biomarkers are important prognostic and predictive indicator, and are routinely tested for in all invasive breast carcinomas.

The ER is a nuclear sex steroid receptor (SSR) that is expressed in the bulk of breast cancers. A proximately 75% of all breast cancers express ER and/or PR, whereas up to 20% of breast cancer display an overexpression/amplification of HER2. Approximately 50% of all Her2-overexpressing breast cancer reveal the coexistence of both HER2 overexpression/amplification and ER and/or PR overexpression. Several in vitro and in vivo studies suggest the presence of a cross-talk between their downstream pathways, which appear to influence the natural history, response to therapy and outcome of patients diagnosed by this subset of breast cancer.

ER-positive breast cancer are regarded in term of prognosis as more favorable than ER-negative breast cancers, whereas HER2/neu-positive tumors are associated with poorer prognosis. With regard to the status of ER-positive and ER-negative in association with epigenetic changes in breast cancer-related genes, it was well established that there was significant differences in tumor-related gene methylation patterns relevant to ER and HER2/neu status of breast cancer. Hyper-methylation, which is an epigenetic alteration that turns off the gene promoter region leading to gene silencing. Silencing of breast cancer related genes by hypermethylation was reported to play a significant role in breast cancer carcinogenesis and progression.

Status in KSA: Several studies has been conducted in this context with diverse findings. A pilot study to screen the main segments of the BRCA1 and BRCA2 genes for disease-associated mutations in Arab and Asian women with breast cancer from the KSA has found that BRCA1 and BRCA2 mutations are likely to contribute to the pathogenesis of familial breast cancer in female patients. Another study to determine whether any association
exists between SNPs in breast cancer associated gene 1 (BRCA1) and breast cancer associated gene 2 (BRCA2) and the breast cancer risk. The study revealed that neither BRCA1 nor the BRCA2 studied variant indicate any significant association with the disease. The comparison of mutation profile with other ethnic groups and regions indicated both dissimilarities and similarities representing co-exposure to a single set of risk factors. The dissimilarities might be related to exposure to certain ecological; carcinogens, diverse lifestyle, reproductive pattern, dietary or cultural practices of Saudi Arabian women that require more research. Another study have identified numerous coding single nucleotide variations that were either novel or uncommon affecting genes controlling DNA repair in the BRCA1/2 pathway. The disturbance of DNA repair pathways is very likely to contribute to breast cancer predisposition in the Saudi population.

In Saudi Arabia, studies of breast cancer gene profiling have showed a different gene expression profile compared to the same patients from North American. In one study, included analysis of breast cancer genes (BRCA1 and BRCA2 as well as 21 additional genes) both for Canadian and Saudi patients for known and unknown mutations, which have been involved in breast and ovarian cancer susceptibility. A round 44% of the mutated genes were found to be unique to the Canadian population, hence, about 34% of the mutated genes were found to be unique for Saudi population. Approximately 43% of the unique mutations in 22 genes were not previously reported in the literature. However, about 22.5% of the mutations in 16 genes were found to be common in both populations.

With regard to ER, PR and HER2; there were few studies conducted in Saudi Arabia. Breast cancer expression pattern of ER, PR and HER2 in Saudi females is different from that of Tunisian and Jordanian females population and closer to the expression pattern of Egyptian Lebanese. Iraqi and western countries females. In a study classified 359 breast cancers into 4 molecular subtypes: luminal A (ER, or PR positive and HER2 negative), luminal B (ER and/or PR positive and HER2 positive), HER2-positive (ER and PR negative and HER2 positive), and triple negative (ER, PR, and HER2 negative). The most prevalent subtype was luminal A (58.5%), followed in descending order of frequency by triple negative (14.8%), luminal B (14.5%), and HER2-positive (23.7%).

1.2. High breast cancer associated syndromes

There are several other rare cancer predisposing syndromes associated with an increased breast cancer risk. The most common syndromes are Li–Fraumeni syndrome, Peutz–Jeghers syndrome (PJS), Cowden syndrome (CS) and Nijmegen breakage syndrome (NBS) and Lynch syndrome.

Breast cancer associated with mutation in TP53 gene and mutation at CHK2 is frequently associated with Li–Fraumeni syndrome. The loss of heterozygosity at the CHK2 gene is frequently associated with Li–Fraumeni syndrome (NBS) and Lynch syndrome. Cowden syndrome (CS) and Nijmegen breakage syndrome (NBS) and Lynch syndrome.

Breast cancer associated with germline mutation in STK11 (LKB1) gene on chromosome 19p is commonly linked to PJS and causing polyposis syndrome. STK11 gene encode a tumor suppressor enzyme (serine kinase 11), which promotes apoptosis, support polarization of tissues and define a cell energy. Moreover, loss of heterozygosity on chromosome p19 is usually associated with familial breast cancer. However, there was only one study from Saudi Arabia linked this gene mutation to gestational diabetes mellitus.

CS is associated with inherited autosomal dominant germline mutation in Phosphatase and Tensin homology (PTEN) gene, which is a tumor suppressor gene. PTEN gene mutation is associated with up to 50% of breast cancers, particularly among elder population.

PTEN gene encode an essential tumor suppressor in the phosphatidylinositol 3-kinase pathway. A sequence analysis of PTEN in BRCA1/BRCA2 mutation-negative individuals failed to detect mutations in the coding region of PTEN, however four variants in intronic sequences were found that do not seem to alter RNA splicing or PTEN protein levels. On the other hand, it was found that PTEN expressing loss in basal like breast cancer is associated with somatic PTEN coding mutations in BRCA1 wild type, and in PTEN mutations related to intragenic chromosome breaks, inversions, deletions and microcopy number aberrations in heterozygous BRCA1 mutation carriers. However, patients attending with CS without PTEN disorder may be linked to genetic heterogeneity. In 22 patients with CS and without PTEN pathogenic variant, the whole-exome sequencing revealed no novel candidate gene, but two patients revealed the presence of previously undescribed Alu insertions with the same break points in exon 5. Notably, such insertions were not found in breast carcinomas that showed a loss of PTEN expression without a detectable alteration of PTEN gene. No such report from Saudi Arabia.

NBS is an autosomal recessive syndrome associated with an increased risk of breast cancer (3 folds), particularly for heterozygous female carriers. NBS is linked to chromosomal instability, which represent as a predisposition to several cancers. Mutations in NBS known to be involved in DNA repair. Lynch syndrome (Hereditary nonpolyposis colorectal cancer (HNPCC)) is an autosomal dominant genetic disorder that has a high risk of colon cancer as well as other cancers due to inherited mutations in mismatch repair (MMR) genes. The frequently reported altered genes include MLH1, MSH2, MSH6, and MLH3, other MMR-associated genes.

Some studies reported a higher breast cancer risk in HNPPC, whereas, other studies showed no or only a slightly elevated breast cancer risk. No such report from Saudi Arabia.

Breast cancer associated with mutation in STK11 (LKB1) gene on chromosome 19p is commonly linked to PJS and causing polyposis syndrome. STK11 gene encode a tumor suppressor enzyme (serine kinase 11), which promotes apoptosis, support polarization of tissues and define a cell energy. More
mutation relatively elevate among those under age of 50 years old. To explain the poor survival No such report from Saudi Arabia.

1.3. DNA repair associated genes

Breast cancer predisposition genes in high-risk families focused on genes involved in DNA repair such as CHEK2, RAD50, BRIP1 and PALB2. Homozygous mutations in BRCA2 that related to DNA repair and predisposition to breast cancer was linked to some autosomal disorders, such as Fanconi anemia or other rare autosomal recessive. Mutations in genes associated with an elevated breast cancer risk in monoaletic mutation carriers cause unusual subgroups of Fanconi anemia, if both alleles are influenced.

*The ATM gene*; is located at 11q22.3, and encodes a protein kinase that plays a significant role in the activation of cellular responses to DNA double-strand breaks through subsequent phosphorylation of central players in the DNA damage-response pathway. ATM mutations are recognized to cause ataxia telangiectasia and a susceptibility to malignancy.

It was well confirmed that some specific variants in the ATM gene are associated with increased breast cancer risk. Amplified breast cancer risk in heterozygous mutation carrier females has been controversial for many years. Previous large epidemiological and molecular studies have provided conclusive evidence that ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. ATM is be classified as a breast cancer susceptibility gene with intermediate penetrance.

*CHEK2 gene* encode checkpoint kinase 2 protein product, which is localized in chromosome 22q12. CHEK2 appears as an essential signal transducer of cellular responses to DNA damage and a candidate tumor suppressor whose defects contribute to molecular pathogenesis of miscellaneous malignancies, both sporadic and hereditary. The CHEK2 mutation deliberates to some extent increased breast cancer risk, but in a familial breast cancer setting this risk is between 35 and 55% for first degree female carriers. Female breast cancer patients with the CHEK2*1100delC mutation are at increased risk of contralateral breast cancer and may have a less favorable prognosis. Female heterozygous CHEK2*1100delC mutation carriers are offered annual mammography and specialist breast surveillance between the ages of 35–60 years.

No such report from Saudi Arabia.

*BRIP1 gene* encode BRCA1 interacting C-terminal helicase 1, which is a target of germline cancer-promoting mutations particularly in the BRCT repeats of BRCA1. Consequently it is vital for the ordinary double-strand repair function of BRCA1. BRIP1 has been suggested to be a low-penetrance breast cancer predisposing gene. Although, BRIP1 gene mutation has been linked to a moderate risk for ovarian cancer, but the role of BRIP1 gene in the pathogenesis of breast cancer is still controversial, though minor effects cannot be excluded. Moreover, a recent study has suggested that BRIP1 can plausibly have an oncogenic role in sporadic cancers.

*PALB2 gene*, which binds and localizes BRCA2 in DNA Repair, is associated with about 2% familial breast cancer. PALB2 mutation is recognized as a moderate-risk breast cancer predisposition gene. PALB2 (FANCN) and BRCA2 (FANCD1) are Fanconi anemia (FA) genes that function in the FA-Breast Cancer DNA repair pathway. The PALB2 gene product functions as a tumor suppressor and interacts closely with both BRCA1 and BRCA2 during double-strand DNA repair. PALB2 mutation carriers seem to have a two-to four-fold relative risk of developing breast cancer; nevertheless, these risk estimates may be even higher in those patients with a family history of breast cancer. PALB2-related breast cancers show a more aggressive tumor phenotype, comprising triple-negative disease, higher tumor grade and higher Ki67 expression. Approximately 40% of the PALB2-related breast cancers recognized to date show a triple-negative phenotype, irrespective of the specific PALB2 mutation.

*RAD50 gene*: The protein complex including Mre11, Rad50, and Nbs1 (MRN) functions in DNA double-strand break repair to identify and process DNA ends as well as signal for cell cycle arrest. Amino acid sequence similarity and overall architecture make RAD50 a member of the structural maintenance of chromosome (SMC) protein family. Functional studies reveal that DNA binding to RAD50 is not critical for DNA double-strand break repair but is essential for telomere maintenance. RAD50 gene mutation usually stop the cells (with damaged DNA) from repairing damaged DNA. Therefore, it has been related to a greater risk of breast cancer in some families. No such report from Saudi Arabia.

1.4. Susceptibility polymorphisms (SNPs) within genes

In recent years, a number of studies have reported that some gene polymorphisms could influence the susceptibility to breast cancer, such as FGFR2, TOX3, LSP1, MAP3K1, and TGFBI. Genomic wide association studies (GWAS) have identified low penetrance and high frequency SNPs that contribute to genetic susceptibility of breast cancer.

*FGFR2 gene*: fibroblast growth factor receptor 2. One of the common low-penetrant genes, has been recognized as a potential breast cancer predisposition gene, which encodes a tyrosine kinase receptor that is a member of the family of exclusively distinctive FGFRs involved in tumorigenesis. FGFR2 is amplified and overexpressed in breast cancer. Results of a meta-analysis indicated that five functional polymorphisms (rs2981579, rs2981582, rs1219648, rs2420946, and rs2912778) in the promoter of FGFR2 gene are associated with breast cancer susceptibility. No such report from Saudi Arabia.

*TOX3 gene*: The human genomic locus for the transcription factor TOX3 has been implicated in susceptibility to restless legs syndrome and breast cancer in genome-wide association studies, but the physiological role of TOX3 remains largely unknown.

*TOX3 gene mutation* (single-nucleotide polymorphisms (SNPs)) was reported to be associated with breast cancer with strong association with ER-positive tumors. Therefore, TOX3 has a strong correlation with the development of breast cancer. GWAS have recognized low penetrance and high frequency SNPs that contribute to genetic susceptibility of breast cancer. The SNPs at 16q12, close to the TOX3 and CASC16 genes, represent one of the susceptibility loci identified by GWAS, displaying strong evidence for breast cancer association across various populations. No such report from Saudi Arabia.

*LSP1 gene* is located on chromosome 11p15.5 and expressed in endothelial and hematopoietic cells. LSP1 rs5695550 and rs592373 polymorphisms may be closely correlated with the occurrence of breast cancer. LSP1 is associated with many other conditions rather than breast cancer. However, the association between LSP1 polymorphisms and the development of breast cancer was infrequently reported. No such report from Saudi Arabia.

*MAP3K1 gene*: the mitogen-activated protein kinase kinase 1 (MAP3K1) gene provides instructions for making a protein that helps regulate signaling pathways that control various processes in the body. MAP3K1 mutations were reported in a variety of cancers with breast cancer being the most frequent one. However, the presence of MAP3K1 in different malignancies with various phenotypes can inspire possible therapeutic targeting of cancer cell associated with gained or lost function of MAP3K1. No such report from Saudi Arabia.
TGFB1 gene: The transforming growth factor beta-1 (TGFB-1) controls the cell growth, proliferation, differentiation, motility and the self-destruction of cells (apoptosis). TGF-β, a super family of growth factors has shown implicated in the regulation of cellular and molecular processes which have involved in cancer initiation and promotion. The double influence of TGFB-1 on the carcinoma-genesis such tumor suppressor in initial phases and tumor promotion and metastasis spread in advanced stages of breast cancer has been proved in several studies.

Mutations in the NBN gene, which commonly result in Nijmegen breakage syndrome, which may increase the susceptibility to many diseases, including breast cancer. NBN are intermediate-risk breast cancer susceptibility genes. No such report from Saudi Arabia.

In conclusion: The majority of cases of breast cancer now a days might be due to a mutation in one or more of the highly penetrant breast cancer genes (BRCA1 BRCA2, TP53, STK11, PTEN, CDH1, NFI or NBN mutations). Mutations in DNA repair associated genes (ATM, CHEK2, BRIP1, PALB2 and RAD50) are associated with elevated breast cancer risk. SNPs were considered as breast cancer susceptibility polymorphisms within genes (TGFB2, TOX3, LSP1, MAP3K1, and TGFB1). Risk prediction models incorporating family history, lifestyle factors and available genetic information may permit suitable preventive management. Screening programs based on genetic information will lead to diminished breast cancer related mortality. Mutation testing presently needs a high index of suspicion for a specific donating etiology, but next-generation sequencing may improve the detection of such genes with their appropriate clinical management. In Saudi Arabia, with exception of BRCA1 BRCA2, TP53, there is a complete absence of literature regarding the susceptibility of these genes. Therefore, we hope that this review can stimulate further studies to assess the exact burden of these genes in the etiology of breast cancer in Saudi Arabia.

Conflicts of interest

Author declares no conflict of interest.

References


