

A systematic review: breast cancer susceptibility genes

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Abstract. Breast cancer is the dominant female cancer and the top cause of cancer deaths in women among the world. The susceptible genes are critical risk factors for both hereditary and sporadic breast cancers. The incidence of carcinoma for carriers with mutated relative genes might increase in comparison with that of the normal population. These genes might be applied in breast cancer populated screening and clinical treatment, in order to improve survival of the breast cancer patients. This study concluded some genes involved in various key elementary processes in cell life, including DNA repair, cell cycle regulation, cell-to-cell adhesion and metabolism, in previous research.

1 Introduction

Breast cancer is the most commonly occurring cancer and the dominant cause of cancer deaths in female around the world. It is estimated that there are 2,088,849 new cases (11.6% in all female cancers) and 626,679 deaths for breast cancer (6.6% in all female cancer deaths) in 2018 among 20 regions all over the world. [1] Certainly, breast cancer is a serious disease burden to the whole society's financial and medical system.

The diagnosis and cure of breast cancer in an earlier stage is significant in improving the survival rate. Women with early stage breast cancer might suffer less risk in operations and are candidates for breast-conserving surgery with radiotherapy or mastectomy. The five-year survival rate of breast cancer in early stage exceeds 80%, with that of advanced breast cancer decreases drastically to less than 30% [2]. To screen breast cancer in population effectively, the detection of risk factors and the selection of high-risk groups are important.

The well-established risk factors for breast cancer include increasing age, female reproductive history, earlier age of menarche and delayed menopause, as well as the history of benign hyperplastic breast disease, life style related factors and genetic factors[3, 4]. It is estimated that mutations in susceptibility genes account for about 20~25% hereditary breast cancer incidences.[5] Some genes, such as BRCA1/2 alone, have been used in breast cancer screening and clinical therapies. However,

the genesis of breast cancer is usually accumulative mutations of several genes. The single gene mutation test may be insufficient to indicate the risk of breast cancer in female. Multi-genes might be expected to apply in future populated screening, DNA counseling and treatment targeting specific genes. This study assembled several breast cancer susceptibility genes in recent studies and categorized them by ways of cancer genesis.

2 The possible molecular oncogenesis of breast cancer

Previous research has defined ten hallmarks of cancer including the maintenance of proliferated signals, resistance for cell deaths, evasive growth suppressors, inducements of angiogenesis, activation of invasion and metastasis, inception of replicate immortality, deregulation of cellular energetics, the avoidance of immune destruction, genome instability, and tumor-promoting inflammation[6]. The cell canceration is a series of accumulated gene mutations, during which the breast cells acquire the ability of endless proliferation and metastasis. These outcomes of gene variants might be direct DNA damage, dysfunction of DNA repairing, dysregulation of cell cycle, less adhesion among adjacent cells[7], abnormal metabolism[8] and epigenetics changes[9]. According to the above mutations contributing to the genesis of breast cancer, we assembled some breast cancer susceptibility genes involved in key processes in cell life (table 1).

Table1. the breast cancer susceptibility genes

Categories	Genes	Mechanism
DNA repairing genes	BRCA1/2	DNA double-strand breaks repair [10]
	PALB2	Recruitment BRAC2 to sites of DNA double-strand breaks [13]

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	RAD51	Forming a nucleoprotein filament on the single-stranded DNA ends [16]
	MLH1 /MSH2	Correcting the DNA mismatch progress [19]
Cell cycle regulation genes	TP53	Forming a homotetramer binding to TP53 response elements in DNA [21]
	PTEN	Inhibiting of the DNA proliferation at the G1-S transition [24]
	DNAH11	Activating of p38 mitogen-activated protein kinase (MAPK) pathway [28]
	CDKN2A/B	Inhibiting of the DNA proliferation at the G1-S transition [30]
	MICA	Modulation in immune response regulation for cell cycles [31]
Cell-to-cell adhesion genes	CDH1	Coding E-cadherin adhesion protein [32]
Metabolism genes	PON1	Coding a multifactorial antioxidant enzyme [35]
	ABC	Encoding large membrane proteins relating the energy dependent transport of xenobiotics [38]

3 Breast cancer susceptibility genes

3.1 DNA repairing genes

3.1.1 Breast cancer susceptibility gene 1 and 2 (BRCA1 and BRCA 2)

BRCA1/2 proteins are involved in repairing damaged DNA as tumor suppressors. By helping mend breaks in DNA, the BRCA1/2 proteins are critical for maintaining the stability of cell's genetic information, which prevents cells from uncontrolled growing and dividing. Most hereditary breast cancers correlate with BRCA1/2 pathogenic mutations. The loss of function in BRCA1/2 might lead to the homologous recombination deficiency, a high-fidelity DNA repair pathway, which finally deprives cells from the ability of DNA double-strand breaks repair. BRCA1/2 mutations account for approximately 35% and 25% hereditary cancers respectively. The pathogenic variants of BRCA1 increase the risk of developing breast cancer by age 70 to 44%~78%, with that of BRCA2 increasing to 31%~56%[10]. Two cohort studies by Engel and Fischer[11] indicated that the cumulative risk of first-time breast cancer at age 60 was 61.8% for BRCA1 mutation carriers, 43.2% for BRCA2 mutation carriers and 15.7% for non-carriers. Simultaneously, compared to that of normal people, breast cancers with BRCA1 mutations tended to be diagnosed at an earlier age and were more likely to be estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) negative [12]. The triple-negative breast cancer usually is less sensitive to hormone therapies. Therefore, carriers of BRCA1/2 mutations suffer a lower survival rate of breast cancer in comparison to BRCA-negative patients, especially the patients with mutated BRCA1.

3.1.2 Partner and localizer of BRCA2 (PALB2)

As a partner of BRCA2, PALB2 mediates its recruitment to sites of DNA double-strand breaks, generating a signaling pathway that involves the Receptor-associated protein 80 (RAP80), Abraxas and BRCA1 tumor suppressors. Then, PALB2 interacts with BRCA2 and involves in DNA repair by homologous recombination [13]. Dysfunction mutations of PALB2 might induce the loss of restraint on tissue growth, which is a significant cause of hereditary breast cancer. In a study conducted by Antoniou[14], compared with that of general population, the risk of breast cancer for female with PALB2 mutation increased seven to eight times for those younger than 40 years of age, five to seven times for those 40 to 60 years of age, and four times for those older than 60 years of age. The study showed that the relative risk for carries of mutated PLAB2 was more significant in younger age and mean cumulative breast cancer risk by 70 years of age was estimated to be 35%. Sometimes the risk relating to PLAB2 might overlie that of BRCA2. Kun Zhang and colleagues examined 2279 samples of Chinese patients, which indicated that, in the familial and sporadic breast cancer cohort, dysfunction of PALB2 mutation carriers accounted for 1.31% and 0.56% respectively [15].

3.1.3 Recombination protein A (RAD51)

Sited in the same pathway as BRCA1/2, the formation of RAD51 nucleoprotein filament on the single-stranded DNA ends, a process for the homology search and strand invasion steps, is a central step in Homologous recombination [16]. By analyzing the cancer family from Murcia (Southeastern Spain)[17], Sánchez-Bermúdez showed that RAD51C pathogenic mutation was described in a breast cancer and ovarian family (0.7%). In a case-control analysis in breast cancer conducted by Na Li[18], 0.4% of breast cancer patients with loss-of-function variants significantly exceeded the 0.04% of that in controls. The RAD51 mutations particularly were

associated with triple-negative type breast cancer, similar to BRCA1/2.

3.1.4 Others

Immunohistochemical analysis suggested that the loss of Mut L homolog 1 (MLH1) and MutS Homolog 2 (MSH2), two important genes might contribute to breast cancer. These two genes participated in the DNA mismatch progress as a post replication error correction way. There were significant associations between MLH1, $P < 0.001$; OR = 13.8; 95%CI = 4.6-41.1, MSH2 ($P < 0.001$; OR = 14.0; 95%CI = 4.7-42.2) and breast cancer [19]. Ataxia telangiectasia-mutated (ATM) and Checkpoint kinase 2 (CHEK2) are also in the same pathway as the BRCA. When including specific variants in the model, the lifetime breast cancer risk of carriers mutations in ATM and CHEK2 rose dramatically to 56.6% and 55.3% respectively. But the results of present study indicated that it was based on their family cancer history. Meanwhile, female with ATM and CHEK2 did not qualify for breast MRI alone to exclude breast cancer [20].

3.2 Cell cycle regulation genes

3.2.1 Tumor protein 53 (TP53)

As an essential tumor suppressor, the TP53 protein plays an elemental role in the genesis and development of various cancer types, including breast cancer. After the exposure of diverse cellular is stressed, TP53 tumor suppressor might be activated and participate in response to inhibit cancer genesis. Following the activation, TP53 protein serves as a transcription factor and forms a homotetramer binding to TP53 response elements in DNA. These responses might be apoptosis, cell-cycle arrest and DNA repair etc. [21] The risk of breast cancer in women with germline mutations in TP53 gene was up to 85% by age 60. About 5-8% of female with breast cancer diagnosed under 30 years old have germline TP53 gene mutations [22]. Besides, compared to early breast cancers from the Cancer Genome Atlas, mutated TP53 is more frequent in metastatic breast cancer, which is the main cause of breast cancer death and has lower five-year survival rate [23].

3.2.2 Phosphatase and tensin homology deleted on chromosome ten (PTEN)

As a key role in the oncogenic PI3K/AKT/mTOR signaling network, PTEN involves in diverse cellular processes and directly inhibits the activation of the cancer genesis [24]. Mitogenic factors and hormones recruit PI3K to the membrane and convert PI(4,5)P2 to PI(3,4,5)P3, which activates AKT and promotes the G1-S transition. By opposing the AKT, PTEN ceases the cell cycle in the G1-S stage and prevents cells from an aggressive and deadly proliferation [25]. N. Alowiri and S. Hanafy used Real time PCR to quantify expressions of PTEN in fifty female patients with breast cancer, which

indicated that the PTEN mRNA expression was significantly increased in breast cancer tissue compared to the normal one ($P < 0.001$, $Z = 5.362$) [26]. The risk of breast cancer in female with germline PTEN mutations was (67-85%) similar to those with mutations in the BRAC1/2 gene [27].

3.2.3 Others

Dynein axonemal heavy chain 11 (DNAH11) gene is involved in the activation of p38 mitogen-activated protein kinase (MAPK) pathway. This pathway functions in the regulation of cell proliferation in Hela cells [28]. A cohort study conducted by S. Verma and D. Bakshi indicated that the rs2285947 variant of DNAH11 was significantly associated with breast carcinoma (adjusted OR = 1.7, $P = 0.0009$) [29].

As a tumor suppressor, cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) genes inhibit the cell cycle at the G1-S border. By logistic regression, S. Seifi and F. Pouya found that individuals with CC/CG genotypes might have higher risk of breast cancer (OR = 2.8, $P = 0.001$) compared with the normal genotypes [30].

Major histocompatibility complex class I-related chain A (MICA) related to breast cancer by modulating immune response mechanisms through NKG2D receptor activation. N. Ouni and A.B. Chaaben found that MICA showed an association between family history of cancer, especially in younger patients (<40 years), and a Val/Val genotype (OR = 2.03, $P = 0.02$) [31].

3.3 Cell-to-cell adhesion genes

Cadherin-1 (CDH1) is the gene coding for the E-cadherin adhesion protein [32]. E-cadherin is a transmembrane glycoprotein expressed in epithelial tissue. This macro molecule is responsible for calcium-dependent cell adhesion and critical for inhibiting cell invasion by participating the establishment and maintenance of polarized, differentiated epithelial cells and the adhesion to adjacent cells [33]. Family history for breast carcinoma was documented in 40.7 % of the considered probands, and 20.3 % presented a bilateral BC manifestation. These mutations affected different CDH1 gene domains, spanning almost all 16 exons and introns 1-7-13 boundaries [34].

3.4 Metabolism genes

3.4.1 Paraoxonase 1 (PON1)

Paraoxonase 1 (PON1) is a multifactorial antioxidant enzyme with strong lipophilic antioxidant properties and scavenges reactive oxygen by binding to high-density lipoprotein (HDL). PON1 was found to be related to several diseases, including obesity, diabetes mellitus and cancers [35]. The case-control trial conducted by A. Farmohammadi and A. Momeni revealed that the PON1-L55M polymorphism in homozygote (OR = 2.13, $P = 0.018$) and allelic (OR = 1.55, $P = 0.008$) significantly increased

the breast cancer risk[36]. In a meta-analysis based on 43 studies, PON1-L55M was found to be a risk factor in the genesis of breast cancer in the Caucasian and Asian population (OR = 2.19). Meanwhile, PON1-Q192R polymorphisms correlated with the decreased risk in breast cancer in the same population as above (OR = 0.64)[37].

3.4.2 ATP-binding cassette (ABC)

The ATP-binding cassette (ABC) transporter superfamily consists of 48 genes and 7 subfamilies, from ABCA to ABCG, encoding large membrane proteins that are essential in the energy dependent transport of xenobiotics, metabolites and signaling molecules across cell membranes [38]. In a case control study, the real-time PCR indicated patients with ABCG2, C421A, and the CC genotype had a higher risk of breast carcinoma compared with those carrying any A alleles (OR=3.06, P=0.0019) [39].

4 Conclusion

Although some previous studies indicated the positive association between several mutated genes and the genesis of breast cancer, there are still some limitations for these researches. The mechanism of some genes triggering progression of cancer remains unclear. Some of genes lack epidemiological evidence about their correlations with breast cancer in large groups. Moreover, only few of above genes, such as BRCA1/2, PTEN and TP53 have been applied in large scale screening for high-risk groups and targeted therapies. More susceptible genes are expected to help the earlier diagnosis of breast cancer and targeted treatments, which might be beneficial to the prevention and cure of the disease. Thus, it is vital to find the mechanism of genetic oncogenesis and deeper connections between susceptibility genes and breast cancer.

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