



REVIEW ARTICLE

Impacts of Genetic Polymorphisms on Breast Cancer

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Abstract

Breast cancer (BC), a malignant proliferation of the epithelial cells that line the ducts or lobules of the breast, is the most common malignancy in women, accounting for approximately one-third of all cancers in women worldwide. According to its death rate, it is the second most frequent cancer causing mortality for women worldwide. Polymorphism involves one of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variation at a single base pair. In recent years there has been an enormous effort by to identify genetic mutations that play a major role in genetic predisposition to and disease progression in particular cancers. This approach has met with considerable success, as exemplified by numerous studies in cancers. In this review we summarize the correlation between genetic polymorphisms and susceptibility to breast cancer.

Keywords

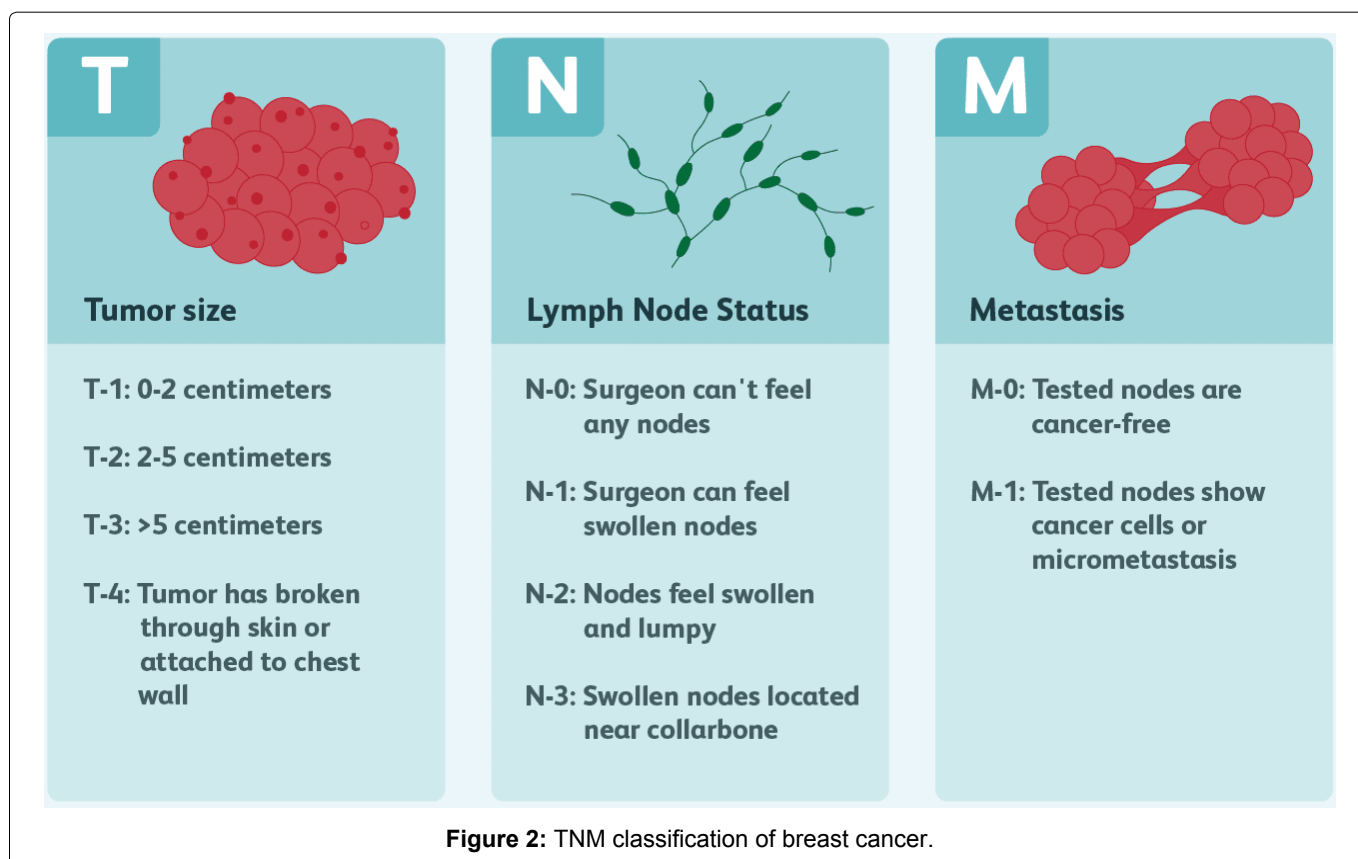
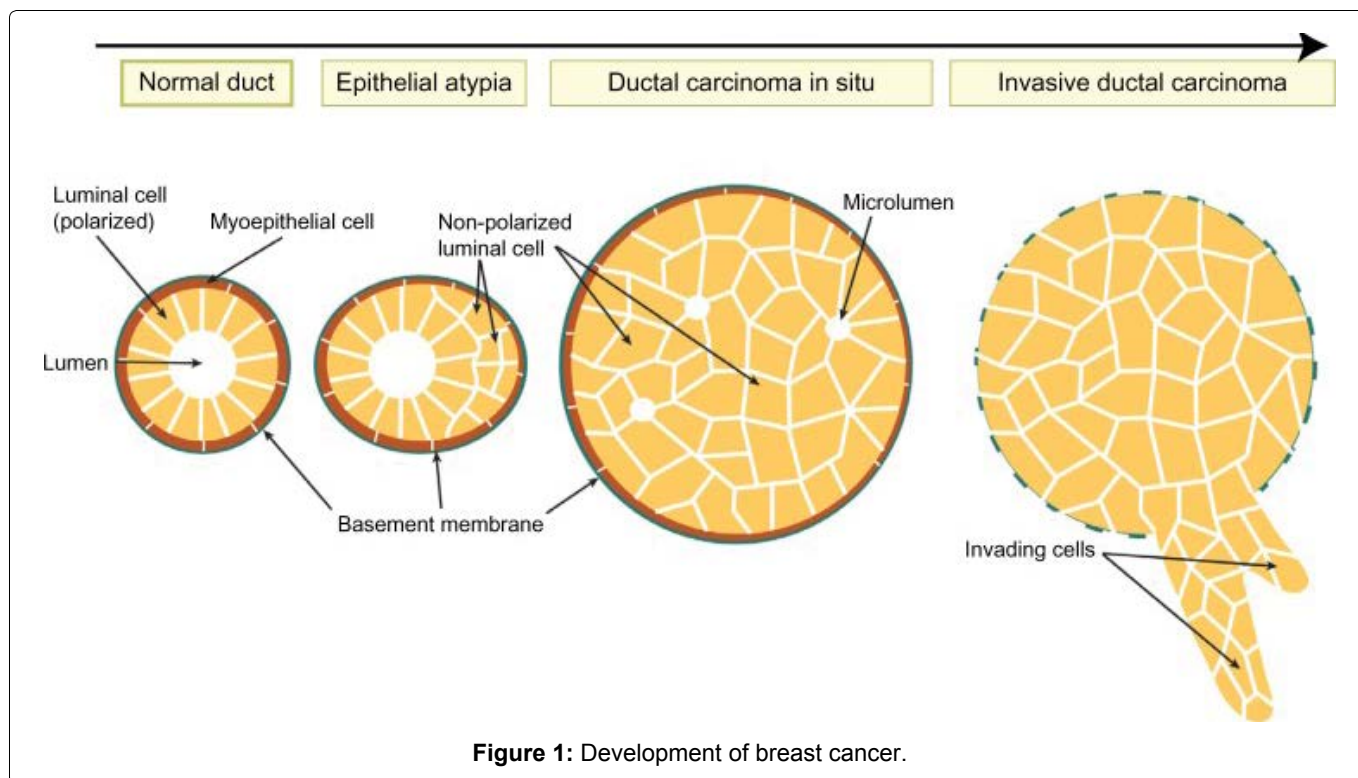
Breast cancer, gene polymorphism

Introduction

Breast cancer is the most common cancer diagnosed in women, accounting for more than 1 in 10 new cancer diagnoses each year. It is the second most common cause of death from cancer among women in the world. Breast cancer always evolves silently. Breast cancer, a highly penetrant hereditary disorder, is the most common cancer in women worldwide. Approximately 10% of breast cancer cases are hereditary and 15% of patients with invasive breast cancer have a first-degree relative with the same disorder. Genetic counseling has become an important tool of the health care system providing information and support to families at risk of a genetic disorder. Most of the patients discover their disease during their routine screening. Others may present with an accidentally discovered breast lump, change

of breast shape or size, or nipple discharge. However, mastalgia is not uncommon. Physical examination, imaging, especially mammography, and tissue biopsy must be done to diagnose breast cancer. The survival rate improves with early diagnosis. The tumor tends to spread lymphatically and hematologically, leading to distant metastasis and poor prognosis. This explains and emphasizes the importance of breast cancer screening programs. Breast cancer can be invasive or non-invasive according to its relation to the basement membrane. Noninvasive neoplasms of the breast are broadly divided into two major types, lobular carcinoma *in situ* (LCIS) and ductal carcinoma *in situ* (DCIS). LCIS is regarded as a risk factor for the development of breast cancer. LCIS is recognized by its conformity to the outline of the normal lobule, with expanded and filled acini. DCIS is more morphologically heterogeneous than LCIS, and pathologists recognize four broad types of DCIS: Papillary, cribriform, solid, and comedo. DCIS is recognized as discrete spaces filled with malignant cells, usually with a recognizable basal cell layer composed of presumably normal myoepithelial cells. The papillary and cribriform types of DCIS are generally lower grade lesions and may take longer to transform into invasive cancer [1,2] (Figure 1).

Genetic polymorphism is a difference in DNA sequence among individuals, groups, or populations. Sources include single nucleotide polymorphisms (SNPs), sequence repeats, insertions, deletions, and recombinations (e.g. a genetic polymorphism might give rise to blue eyes vs. brown eyes, or straight hair vs. curly hair). Genetic polymorphisms may be the result of chance processes, or may have been induced by external agents such as viruses or radiation. If a



difference in DNA sequence among individuals has been shown to be associated with disease, it will usually be called a genetic mutation. Changes in DNA sequence that have been confirmed to be caused by external agents are also generally called 'mutations' rather than 'polymorphisms'. Most common polymorphisms are potential regulatory polymorphisms located in noncoding regions, including promoter/upstream, downstream and intron regions that may affect

transcription [3] (Figure 2).

Tissue inhibitor of metalloproteinase-2 (TIMP-2) polymorphism

Tissue inhibitor of metalloproteinase-2 (TIMP-2) is an endogenous inhibitor of MMP-2 that has been implicated in the regulation of MMP-2 proteolytic activity through formation of a 1:1 stoichiometric inhibitory complex with the enzyme [4]. Genetic polymorphisms in the

TIMP-2 gene, located on chromosome 17q25, may lead to an increase or decrease in TIMP-2 activity and subsequently disrupt the balance between the activity of TIMP-2 and MMP-2. This disrupted balance could then influence cancer development and progression [5]. TIMP-2 is expected to serve as an anti-invasive/anti-metastatic agent through inhibition of MMP-2. Changes in the level of TIMP-2 are known to directly affect the activity level of MMP-2 [6]. One research explore the association between TIMP-2 and breast cancer, and found that TIMP-2 rs7501477 and rs8064344 mutation affects the genetic susceptibility of breast cancer; while, no effect of rs2277698 mutation on breast cancer was found [7]. A previous study suggested that mutations in the rs4789936 locus not only affect the genetic susceptibility of breast cancer, but also affect the survival of breast cancer patients [7]. So, the role of rs4789936 mutation on the genetic susceptibility of breast cancer remains controversial.

RETN genetic polymorphism

The prognosis of breast cancer patients depends on the clinical or pathological stage at diagnosis. Thus, individuals with hereditary breast cancer could benefit from epigenetic screening for early diagnosis and treatment that prevents the disease from developing. RETN polymorphisms have been identified in various cancers, including colon and lung [8-10]. SNP rs3219175 and rs7408174 at greater risk of developing RA disease [11], and the effects of these variants on resist in expression require to be further examined in breast cancer cells in the future. A previous study has reported that the rs1862513 SNP in RETN increased breast cancer risk and a tendency for luminal breast tumors in Mexican women, which divided into different subtypes according to BMI [12].

Polymorphism of XRCC3

The X-ray repair cross-complementing group 3 genes (XRCC3) belongs to a family of genes responsible for homologous recombination, repairing DNA double-strand breaks (DSBs) and interstrand cross-links caused by normal metabolic processes and exposure to ionizing radiation [13]. The XRCC3 gene is structurally and functionally related to the RAD51 gene, which is known to play an important role in all three stages of homologous recombination and catalyzes the invasion of broken ends of the DSB into the intact sister chromatid. Moreover, XRCC3 takes part in DSB repair as it causes slowing of DNA synthesis and recruitment of RAD51 at repair sites [14]. Studies that revealed that polymorphisms in the XRCC3 (rs861539) gene were significantly associated with an increased risk of BC were conducted in different ethnic populations, and the results are inconsistent with our findings, which may be due to environmental factors, ethno-cultural variations, and/or variations in linkage disequilibrium of the XRCC3

gene [15-17].

Polymorphism of DNA repair genes

DNA repair is a part of the barriers, protecting from cancer forming mutations [18,19]. Following the results of studies, cancer diseases are driven by a compromised ability of DNA repair. Therefore, a set of alleles of repair protein encoding genes may largely define the individual abilities for DNA damage repair, as well as the susceptibility to tumor development. It is then important to learn the polymorphic variants of the genes, associated with DNA repairs, as well as with their degradation in their population. The single nucleotide polymorphisms (SNPs) may change the risk of cancer. SNPs may then be regarded as potential markers of carcinogenesis [20,21]. The Asp allele of Gly322Asp polymorphism was strongly correlated with breast cancer. The Gly322Asp polymorphism affected the tumor grade and size, as well as was associated with the lymph node status. As literature data demonstrate DNA damages to be highly significant in the pathogenesis of breast cancer, especially those which require repair by homologous recombination [22,23].

FSCN1 gene polymorphisms

FSCN1, a 55-kDa cytoskeletal actin-binding protein that packages actin filaments into tertiary structures, including microspikes, stress fibers and membrane ruffles, within dynamic cellular structures, enhances cell motility, migration and adhesion. Upregulation of FSCN1 has been indicated in various cancer cell types such as stomach, colon, lung, ovary and breast [24,25]. Fascin expression plays a central role in regulating breast cancer cell morphology, migration and invasion potential [24]. Inhibition of FSCN1 reduces cancer migration and tumor metastasis in prostate and oral squamous cancer cells [26,27]. Furthermore, docosahexaenoic acid reduces FSCN1-dependent breast cancer metastasis [25]. These results suggest that knockdown FSCN1 might be a valuable therapeutic strategy for breast cancer. The human tumor suppressor gene p53 encodes a transcription factor, playing a central role in maintaining cellular integrity by the inhibition of cell growth and stimulation of apoptosis in response to DNA damage. Its role in cancer development is widely studied and well documented [28]. A common single nucleotide polymorphism (SNP) is known in the second position of codon 72 at exon 4 (rs1042522 – CCC to CGC), resulting in a substitution of proline (Pro) to arginine (Arg) in the Pro-rich region [29]. The meta-analysis conducted by Gonçalves, et al. [30] showed that breast cancer patients and control subjects were mainly heterozygous in the Asian population (50.1 and 48.0%, respectively) and the African population (43.9 and 49.7%, respectively), whereas the homozygote Arg/Arg was predominant in America (53.6 and 54.5%, respectively) and Europe (54.1 and 53.4%, respectively). However, the Pro/Arg

heterozygous genotype was found to be higher in a Saudi population among healthy women (60.19%) than in women with breast cancer (25%) [31], while the Pro/Arg genotype has been reported to be associated with breast cancer risk in an Iranian population, with 75.55% in breast cancer cases versus 62% in controls [32].

BRCA1 polymorphism and BRCA2 -26G>A 5' untranslated region polymorphism

BRCA1 and BRCA2 are structurally similar and of similar size (100 and 70 Kb, respectively). The two genes are considered to be tumor suppressor genes. BRCA1 is located on chromosome 17 at the q21 position and consists of 22 exons (60% of the gene corresponding to exon 11) that encode a protein of 1,863 amino acids. Due to its large size, exon 11 is the main target for mutation detection. BRCA2 is located on chromosome 13 at the 12q position and consists of 27 exons that encode a protein of 3,418 amino acids [33,34]. It is extremely important to perform genetic analysis for BRCA mutations in patients at a high risk of developing breast cancer in Argentina to aid health professionals in addressing the prevention, treatment and prognosis of the disease [35,36]. A recent study has yielded encouraging results on the development of a test gene expression profile from the peripheral blood for the early detection of breast cancer with a prediction accuracy of 79.5%, sensitivity of 80.6% and specificity of 78.3% [37]. The -26 G>A polymorphism in the 5' UTR of BRCA2 has been analyzed in some cancer types. Another study showed a monotonic increase in the frequency of the heterozygous G/A genotype from the lowest to highest risk groups of esophageal squamous cell carcinoma from northern China [38].

Acknowledgment

The author would like to thank Professor/Hafez Ahmed, professor of Biochemistry, Dubai Medical College for his support.

References

- Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP (2018) Local Cancer Recurrence: The Realities, Challenges, and Opportunities for New Therapies. *CA Cancer J Clin* 68: 488-505.
- Cain EH, Saha A, Harowicz MR, Marks JR, Marcom PK, et al. (2019) Multivariate machine learning models for prediction of pathologic response to neoadjuvant therapy in breast cancer using MRI features: A study using an independent validation set. *Breast Cancer Res Treat* 173: 455-463.
- Chorley BN, Wang X, Campbell MR, Pittman GS, Nouredine MA, et al. (2008) Discovery and verification of functional single nucleotide polymorphisms in regulatory genomic regions: Current and developing technologies. *Mutat Res* 659: 147-157.
- Visse R, Nagase H (2003) Matrix metalloproteinases and tissue inhibitors of metalloproteinases: Structure, function, and biochemistry. *Circ Res* 92: 827-839.
- Srivastava P, Lone TA, Kapoor R, Mittal RD (2012) Association of promoter polymorphisms in MMP2 and TIMP2 with prostate cancer susceptibility in North India. *Arch Med Res* 43: 117-124.
- Remacle A, McCarthy K, Noel A, Maguire T, McDermott E, et al. (2000) Foidart JM, Duffy MJ. High levels of TIMP-2 correlate with adverse prognosis in breast cancer. *Int J Cancer* 89: 118-121.
- Peterson NB, Beeghly-Fadiel A, Gao YT, Long J, Cai Q, et al. (2009) Polymorphisms in tissue inhibitors of metalloproteinases-2 and -3 and breast cancer susceptibility and survival. *Int J Cancer* 125: 844-850.
- Alharithy RN (2014) Polymorphisms in RETN gene and susceptibility to colon cancer in Saudi patients. *Ann Saudi Med* 34: 334-339.
- Hu WW, Tang CH, Sun Y, Lu TT, Jiang P, et al. (2017) Correlation between resistin gene polymorphism and clinical aspects of lung cancer. *Medicine (Baltimore)* 96: e9485.
- Vallega KA, Liu N, Myers JS, Yu K, Sang QX (2016) Elevated Resistin Gene Expression in African American Estrogen and Progesterone Receptor Negative Breast Cancer. *PLoS One* 11: e0157741.
- Wang L, Tang CH, Lu T, Sun Y, Xu G, et al. (2018) Resistin polymorphisms are associated with rheumatoid arthritis susceptibility in Chinese Han subjects. *Medicine (Baltimore)* 97: e0177.
- Munoz-Palomeque A, Guerrero-Ramirez MA, Rubio-Chavez LA, Rosales-Gomez RC, Lopez-Cardona MG, et al. (2018) Association of RETN and CAP1 SNPs, Expression and Serum Resistin Levels with Breast Cancer in Mexican Women. *Genet Test Mol Biomarkers* 22: 209-217.
- Hu J, Wang N, Wang Y-J (2013) XRCC3 and RAD51 expression are associated with clinical factors in breast cancer. *PLoS One* 8: e72104.
- Pelttari LM, Kiiski JI, Ranta S, Vilske S, Blomqvist C, et al. (2015) RAD51, XRCC3, and XRCC2 mutation screening in Finnish breast cancer families. *Springerplus* 4: 92.
- Al Zoubi MS, Zavaglia K, Mazanti C, Hamad MA, Batayneh KA, et al. (2017) Polymorphisms and mutations in GSTP1, RAD51, XRCC1 and XRCC3 genes in breast cancer patients. *Int J Biol Markers* 32: 337-343.
- Sanjari Moghaddam A, Nazarzadeh M, Noroozi R, Darvish H, MosaviJarrahi A (2016) XRCC1 and OGG1 gene polymorphisms and breast cancer: a systematic review of literature. *Iran J Cancer Prev* 9: e3467.
- Romanowicz H, PyziakŁ, Jabłoński F, Bryś M, Forma E, et al. (2017) Analysis of DNA repair genes polymorphisms in breast cancer. *Pathol Oncol Res* 23: 117-123.
- Broustas CG, Lieberman HB (2014) DNA damage response genes and the development of cancer metastasis. *Radiat Res* 181: 111-130.
- Kurfurstova D, Bartkova J, Vrtel R, Mickova A, Burdova A, et al. (2016) DNA damage signalling barrier, oxidative stress and treatment-relevant DNA repair factor alterations during progression of human prostate cancer. *Mol Oncol* 10: 879-894.
- Erichsen HC, Chanock SJ (2004) SNPs in cancer research and treatment. *Br J Cancer* 90: 747-751.
- Shridhar K, Aggarwal A, Walia GK, Gulati S, Geetha AV, et al. (2016) Single nucleotide polymorphisms as markers of genetic susceptibility for oral potentially malignant disorders risk: review of evidence to date. *Oral Oncol* 61: 146-151.

22. Kwei KA, Kung Y, Salari K, Holcomb IN, Pollack JR (2010) Genomic instability in breast cancer: Pathogenesis and clinical implications. *Mol Oncol* 4: 255-266.
23. Sekhar D, Pooja S, Kumar S, Rajender S (2015) RAD51 135G>C substitution increases breast cancer risk in an ethnic-specific manner: a meta-analysis on 21,236 cases and 19,407 controls. *Sci Rep* 5: 11588.
24. Zhao J, Zhou Y, Zhang Z, Tian F, Ma N, et al. (2009) Upregulated fascin1 in non-small cell lung cancer promotes the migration and invasiveness, but not proliferation. *Cancer Letters* 290: 238-247.
25. Yoder BJ, Tso E, Skacel M, Pettay J, Tarr S, et al. (2005) The expression of fascin, an actin-bundling motility protein, correlates with hormone receptor-negative breast cancer and a more aggressive clinical course. *Clin Cancer Res* 11: 186-192.
26. Darnel AD, Behmoaram E, Vollmer RT, Corcos J, Bijian K, et al. (2009) Fascin regulates prostate cancer cell invasion and is associated with metastasis and biochemical failure in prostate cancer. *Clinical Cancer Research* 15: 1376-1383.
27. Chen SF, Lin CY, Chang YC, Li JW, Fu E, et al. (2009) Effects of small interfering RNAs targeting Fascin on gene expression in oral cancer cells. *J Oral Pathol Med* 38: 722-730.
28. Yue X, Zhao Y, Xu Y, Zheng M, Feng Z, et al. (2017) Mutant p53 in cancer: Accumulation, gain-of-function, and therapy. *J Mol Biol* 429: 1595-1606.
29. Matlashewski GJ, Tuck S, Pim D, Lamb P, Schneider J, et al. (1987) Primary structure polymorphism at amino acid residue 72 of human p53. *Mol Cell Biol* 7: 961-963.
30. Gonçaves M, Borja SM, Cordeiro JA, Saddi VA, Ayres FM, et al. (2014) Association of the TP53 codon 72 polymorphism and breast cancer risk: a meta-analysis. *Springerplus* 3: 749.
31. Al-Qasem A, Toulimat M, Tulbah A, Elkum N, Al-Tweigeri T, et al. (2012) The p53 codon 72 polymorphism is associated with risk and early onset of breast cancer among Saudi women. *Oncol Lett* 3: 875-878.
32. Boroujeni HR, Karimi M, Moshkelani S, Parsaei P (2013) Association of the p53 codon 72 polymorphism with breast cancer in central part of Iran. *African J Pharm Pharmacol* 7: 356-359.
33. Bissonauth V, Shatenstein B, Fafard E, Maugard C, Robidoux A, et al. (2009) Weight History, Smoking, Physical Activity and Breast Cancer Risk among French-Canadian Women Non-Carriers of More Frequent BRCA1/2 Mutations. *J Cancer Epidemiol* 2009: 748367.
34. Brasky TM, Bonner MR, Moysich KB, Ambrosone CB, Nie J, et al. (2010) Non-steroidal anti-inflammatory drug (NSAID) use and breast cancer risk in the Western New York Exposures and Breast Cancer (WEB) Study. *Cancer Causes Control* 21: 1503-1512.
35. Ambrosone CB, Freudenheim JL, Graham S (1996) Cigarette smoking, N-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. *JAMA* 276: 1494-1501.
36. Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, et al. (2008) Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. *J Clin Oncol* 26: 4282-4288.
37. Easton DF, Hopper JL, Thomas DC, Antoniou A, Pharoah PD, et al. (2004) Breast cancer risks for BRCA1/2 carriers. *Science* 306: 2187-2191.
38. Hu N, Li WJ, Su H, Wang C, Goldstein AM, et al. (2003) Common genetic variants of TP53 and BRCA2 in esophageal cancer patients and healthy individuals from low and high risk areas of northern China. *Cancer Detect Prev* 27: 132-138.