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Mini Review

Genetic Contribution to Breast Cancer: A Critical Analysis of Penetrance Alleles as Susceptible Genes

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Abstract

Breast cancer can develop either in the tubes connecting the lobules of milk-producing glands to the nipple or the lobules themselves. GLOBOCAN 2021 reported an estimated 14.1 million new instances of cancer, 8.2 million cancer-related deaths, and 32.6 million people who had cancer for at least five years after their diagnosis. The development of genomic instability enables the acquisition of functional cells to become cancerous allowing the survival, proliferation, and dissemination of malignancy. These cells develop distinctive abilities as a result of acquired rare genetic mutations. Multistep tumor growth is caused by a succession of clonal expansions that are set off by the accidental discovery of an enabling mutant genotype. Hence, it is vital to identify defective genes in breast cancer and breast cancer therapy to mitigate the need for treatment. Critical analyses of various defective genes are compiled in this review.

Introduction

Aberrant structure and copy number aberrations and differential expression patterns of diverse genes are observed in tumor cells.[1] One of the two enabling characteristics for the acquisition of functional capabilities allowing the survival, proliferation, and dissemination of cancer cells is the development of genomic instability (and the second being tumor-promoting inflammation), which causes random mutations including rearrangements of the chromosome. Rare genetic changes among these bring about hallmark capabilities. The succession of clonal expansions triggered by the chance acquisition of an enabling mutant genotype leads to multistep tumor progression.[2] Genomic instability and as a consequence, mutability bestow malignant cells with genetic alterations which lead to tumor progression. To orchestrate tumorigenesis, cancer cells boost the mutation rate either by the collapse of one or numerous components of the genomic maintenance machinery or through increased sensitivity to mutagenic agents, or both.[3] The surveillance system, mainly TP53 (Tumor protein p53), the guardian of the genome that monitors genomic integrity and forces genetically damaged cells into either senescence or apoptosis, is compromised thus accelerating the rate at which mutation accumulates.[4]

Keywords: Breast cancer; Genes; Therapy; Malignancy; Mutation; Phenotype.

Abbreviations: ABRAXAS, abraxas 1, BRCA1-A complex subunit; AKT1, protein kinase B; ATM, ataxia telangiectasia mutated; BARD1, BRCA1-associated RING domain protein 1; BRCA1, breast cancer gene 1; BRCA2, breast cancer gene 2; BRIP, BRCA1 interacting protein C-terminal helicase 1; CDH1, cadherin; CHEK2, checkpoint kinase 2; DNA, deoxyribonucleic acid; FGFR2, fibroblast growth factor receptor 2; GWAS, genome-wide association studies; IBIS, International Breast Cancer Intervention Study; LSP1, lymphocyte specific protein 1; MAP3K1, mitogen-activated protein kinase 1; MRE11A, meiotic recombination 11 homolog A; NBN, nibrin; PALB2, partner and localizer of BRCA2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RAD50, RAD50 double-strand break repair protein; RAD51C, RAD51 paralog C; RAD51D, RAD51 paralog D; RNA, ribonucleic acid; STK11, serine/threonine protein kinase 11; TNRC9, trinucleotide-repeat-containing 9; TP53, tumor protein p53; XRCC2, x-ray repair cross-complementing 2.

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Role of mutations

Breast cancer is a malady where cells become atypical and proliferate to form a malignant tumor. 10–30% of all malignancies are due to hereditary factors whereas only 5–10% of breast cancer cases are recognized with strong inherited components. Small fractions of 4–5% of these cases are due to mutations in the high penetrant autosomal dominantly transmitting genes.[5] The fundamental property of almost all malignant cells is the instability in the genome caused by either inherited or somatic mutation. Genetic alteration can arise at various levels ranging from single nucleotides, microsatellites (small stretches of DNA), whole genes, structural components, or whole chromosomes.[6] Invasive micropapillary carcinoma has been found in almost 2–8% of all breast cancers and pure micropapillary carcinoma accounts for 0.9–2% of breast cancers.[7,8] The mutation in PIK3CA or AKT1 is the main cause of the development of invasive micropapillary carcinoma.[9] Genetic alterations in certain combinations or the development of

mutation in a specific subset of target cells have a greater tendency for malignant development. Genes predisposed to cancer are categorized concerning their relative risk to specific cancer types. High-penetrant, low-penetrant, and intermediate-penetrant genes confer relative cancer risk greater than 5, around 1.5, and from 1.5 to 5 respectively.

Rare high-penetrance alleles

Examples include *BRCA1*, *BRCA2*, *TP53, PTEN* (phosphatase and tensin homolog deleted on chromosome 10), *STK11* (serine/threonine protein kinase 11), *CDH1* (cadherin 1), Disease-causing variants in BRCA1 and BRCA2 confer a 10–20-fold relative risk of breast cancer, which is higher for an early onset of malignancy.[10] It is rare, with a population carrier frequency of ≤ 0.1%. The risk of developing ovarian cancer and other cancers also remains high. These mutations inactivate the encoded proteins by premature truncation of protein or nonsense-mediated RNA decay. Mutations in families predisposed to cancer are transmitted in an autosomal dominant way. At the cellular level, BRCA1 and BRCA2 act as a recessive cancer gene, which on mutations are converted to homozygosity through the loss of wild-type allele.[11] Mutations of BRCA1 and BRCA2, rare high penetrance breast cancer predisposing genes, account for 16–25% of the inherited components of breast cancer. Rare germline mutations in TP53, which causes Li-Fraumeni syndrome; STK11, which causes Peutz-Jeghers syndrome; PTEN, which causes Cowden syndrome; and CDH1 are infrequent causes.[12] Studies have shown that strongly predisposing BRCA1 or BRCA2 mutation contributes to only 15–20% of familial risk, the remaining 80–85% might be attributed to genetic or environmental origin. However, data from various studies suggest that genetic factors predominate in high-risk penetrance alleles.

Rare moderate-penetrance alleles

Examples include *ATM* (ataxia telangiectasia mutated), *BRIP1* (BRCA1 interacting protein C-terminal helicase 1), *CHEK2* (checkpoint kinase 2) (22q12.1), *PALB2* (partner and localizer of BRCA2), *BARD1* (BRCA1-associated RING domain protein 1), *MRE11A* (MRE11 homolog, double-strand break repair nuclease), *NBN* (nibrin), *RAD50* (RAD50 double-strand break repair protein), *RAD51C* (RAD51 paralog C), *XRCC2* (x-ray repair cross-complementing 2), *RAD51D* (RAD51 paralog D), *ABRAXAS* (abraxas 1, BRCA1-A complex subunit) (4q21.23). Inherited mutations in ATM, CHEK2 (checkpoint kinase 2), BRIP1 (BRCA1 interacting protein C-terminal helicase 1), BARD1, and PALB2 (partner and localizer of BRCA2) contribute to an intermediate breast cancer risk.[13] The disease-causing mutations lead to premature protein truncation or non-sense-mediated RNA decay caused by translational frameshifts or nonsense codons. A rare missense variant in a small proportion also disrupts critical functions. Mutations in *ATM*, *CHEK2*, *BRIP1*, *BARD1*, and *PALB*2 confer a 2–3-fold risk of breast cancer and contribute to the familial risk of breast cancer by 2.3%. It is rare with a population carrier frequency of ≤ 0.6%. The disease-causing mutations in these genes resemble the disease-causing mutations in BRCA1 and BRCA2 to a great extent. However, they vary in terms of the risk they confer in the development of breast cancer.[14]

Common low-penetrance alleles

Examples include rs2981582 [*FGFR2* (fibroblast growth factor receptor 2), 10q], rs3803662 [*TNRC9* (trinucleotide-repeat-containing 9) (recently renamed *TOX3* (TOX high mobility group box family member 3), 16q)], rs889312 [*MAP3K1* (mitogen-activated protein kinase 1), 5q], rs3817198 [*LSP1* (lymphocyte specific protein 1), 11p], rs13281615 (8q), rs13387042 (2q), rs1045485 [*CASP8*_D302H (caspase 8)]. Several common breast cancer susceptibility loci follow a polygenic model or operate synergistically with lifestyle or environmental factors. They are found to be associated with increased or decreased risk of breast cancer to some extent and account for a smaller fraction of familial breast cancer cases.[15] They are common with a population frequency of 5–50%. Variants confer a relative risk up to 1.25-fold for heterozygous or 1.65-fold for homozygous. Some of these low-penetrance breast cancer susceptibility polymorphisms have been found to work as modifier genes in carriers of BRCA1/BRCA2 mutation. Studies have also shown that a particular SNP in CASP8 conferred a slightly increased susceptibility.[16] Carriers of two high-risk alleles at the FGFR2 locus have a higher relative risk compared to carriers of one high-risk and one low-risk allele, which in turn have a higher relative risk than two low-risk alleles. An individual carrying various polymorphisms may contribute to a considerably increased risk of breast cancer due to the synergic effect of polymorphisms.[17] The contribution of common low-penetrance susceptibility loci in causing hereditary breast cancer is controversial.

Risk factors of gene mutation

Several factors increase the risk of developing breast cancer including age, which is one of the most important—about 71.2% of the risk is associated with an age above the 60s. Secondly, a person's lifestyle has a considerable influence on their risk of developing cancer; for example, people who regularly drink alcohol and intake fatty foods are at an increased risk of developing cancer. A high level of estrogen can also lead to the development of cancer. Other factors may include delayed menopause, delayed pregnancy, etc. These factors differ from person to person as each individual has a different physiological functioning and lifestyle. The severity and the type of breast cancer highly depend on the types of the gene mutated, as each gene corresponds to the development of different types of cancer as discussed in Table 1.[18–31] The analysis of breast cancer risk for the BRCA mutated population is depicted in Figure 1.

Mathematical models for detecting gene-mediated pathogenic variants in breast cancer

Mathematical models have indeed been developed to assess the risk that an individual carries a pathogenic variant in breast cancer. These models are often used in clinical settings to estimate an individual's likelihood of having a genetic mutation associated with breast cancer, such as mutations in the BRCA1 or BRCA2 genes. These models take into account various factors, including personal and family medical history, age, ethnicity, and other relevant clinical information. They use statistical algorithms and data derived from population studies to calculate an individual's risk based on these factors.[32,33] The models can provide a risk assessment as a numerical probability or a categorization of risk, such as "high," "moderate," or "low." Examples of widely used mathematical models for breast cancer risk assessment include:

Gail model: The Gail model is one of the most commonly used models for estimating a woman's risk of developing breast cancer. It incorporates factors such as age, age at first menstrual period, age at first live birth, number of previous breast biopsies, and family history of breast cancer;

Table 1. Mechanism of action of several breast cancer-related genes, their pathogenesis, and risk

Gene	Mechanism of action	Risk of developing breast cancer	Type of breast cancer	References
Rare high-penetrance alleles				
BRCA1	Cell cycle activation, regulation of transcription, and apoptosis	50–80%	Triple-negative breast cancer	18
BRCA2	DNA repairing (especially in homologous recombination of double-strand DNA breaks)	10–25%	–	19
TP53	Regulate cell cycle, metabolism, apoptosis	100%	HR+ve/HER2-ve breast cancer	20
PTEN	Role in PI3K/AKT-mTOR signaling pathway	30 %	HR+ve/HER-ve breast cancer	21
STK11	Cell cycle regulation, mediation of apoptosis	32–54%	Papillary breast cancer	22
CDH1	Role in cell mortality, differentiation, growth, migration, and signaling	40–50%	Lobular breast cancer	23
Rare moderate-penetrance alleles				
ATM	DNA repairing	Moderate risk	Contralateral breast cancer	24
RAD51	DNA repairing, Cell cycle regulation	-	Invasive ductal breast cancer	25
CHEK2	Regulate p53 function	0.5 – 2%	Contralateral breast cancer; HR+ve breast cancer	26
PALB 2	Regulation of cell growth, cell division, and tumor suppression	0.6–3.9%	Triple-negative breast cancer	27
BARD1	Cell cycle regulation, DNA-repairing	17–30 %	Ductal and medullary breast cancer	28
Rare low-penetrance alleles				
FGFR2	Involve in cell division, cell maturation, formation of new blood vessels	15%	Invasive ductal carcinoma	29
TOX3	Cell cycle regulation	-	HR+ve breast cancer	30
MAP3K1	Regulate signaling pathway	6%	HR+ve /HER-ve breast cancer followed by HR+ve/HER +ve breast cancer	31

ATM, ataxia telangiectasia mutated, BARD1, BRCA1-associated RING domain protein 1, BRCA1, breast cancer gene 1, BRCA2, breast cancer gene 2, CDH1, cadherin, CHEK2, checkpoint kinase 2, FGFR2, fibroblast growth factor receptor 2, MAP3K1, mitogen-activated protein kinase 1, PALB2, partner and localizer of BRCA2, PTEN, phosphatase and tensin homolog, RAD51, RAD51 paralog, STK11, serine/threonine protein kinase 11, TOX3, TOX high mobility group box family member 3, TP53, tumor protein p53.

Claus model: The Claus model is specifically designed to assess the risk of carrying a BRCA1 or BRCA2 mutation. It takes into account family history, including the number of first- and second-degree relatives affected by breast or ovarian cancer;

Tyrer-Cuzick model: The Tyrer-Cuzick model, also known as the International Breast Cancer Intervention Study (IBIS) model, is a comprehensive model that considers various risk factors, including family history, age, reproductive history, and other factors

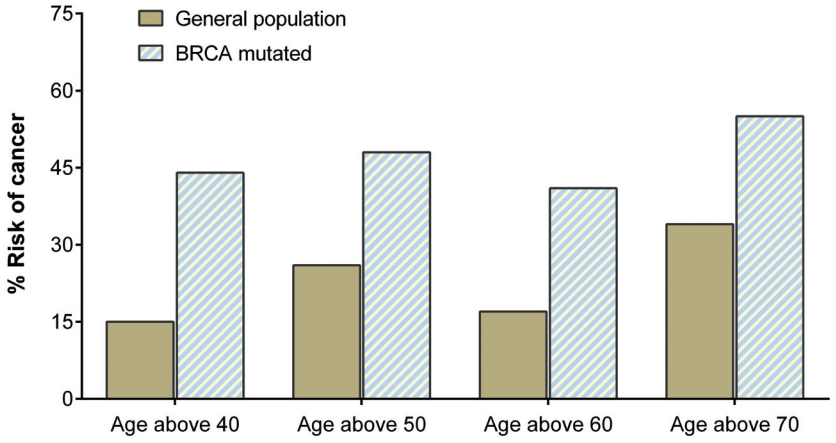

Fig. 1. Risk percentage of breast cancer in normal population and BRCA mutated population. BRCA, breast cancer gene.

related to breast cancer risk.

These mathematical models serve as valuable tools to assist healthcare professionals in identifying individuals who may benefit from genetic testing or targeted interventions for breast cancer risk reduction. However, it is important to note that these models have limitations and should be used in conjunction with clinical judgment and counseling to make informed decisions about individualized care and management.

Future directions

Further identification of susceptible genes: Future research should focus on identifying additional penetrance alleles and susceptible genes associated with breast cancer. Advances in genomic technologies, such as whole-genome sequencing and genome-wide association studies (GWAS), can contribute to a better understanding of the genetic factors influencing breast cancer risk.

Functional characterization of penetrance alleles: Understanding the functional consequences of penetrance alleles is essential for elucidating their role in breast cancer development. Future studies should aim to investigate the molecular mechanisms through which these alleles contribute to tumorigenesis and identify potential therapeutic targets.

Integration of genetic information in risk assessment: Incorporating genetic information, including penetrance alleles and susceptible genes, into risk assessment models can enhance breast cancer prediction. Future directions should explore the integration of genetic markers with clinical factors to improve risk stratification and inform personalized screening and prevention strategies.

Precision medicine approaches: The identification of penetrance alleles and susceptible genes can pave the way for precision medicine approaches in breast cancer. Future research should focus on developing targeted therapies and interventions tailored to individuals based on their genetic profiles, enabling more effective and personalized treatment strategies.

Conclusions

In conclusion, the genetic contribution to breast cancer is complex and multifactorial. Penetrance alleles, as susceptible genes, play a significant role in determining individual susceptibility to the disease. Critical analysis of these alleles provides valuable insights into breast cancer risk assessment and management. However, future research is needed to identify additional susceptible genes, elucidate their functional implications, and integrate genetic information into risk assessment models. The ultimate goal is to advance precision medicine approaches that leverage genetic knowledge to improve breast cancer prevention, diagnosis, and treatment, ultimately leading to better outcomes for affected individuals.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

DS and SK conceptualized the idea and wrote the draft of the manuscript.

References

[1] Martin AM, Weber BL. Genetic and hormonal risk factors in breast cancer. J Natl Cancer Inst 2000;92(14):1126–1135. doi:10.1093/jnci/92.14.1126, PMID:10904085.

[2] Valencia OM, Samuel SE, Viscusi RK, Riall TS, Neumayer LA, Aziz H. The Role of Genetic Testing in Patients With Breast Cancer: A Review. JAMA Surg 2017;152(6):589–594. doi:10.1001/jamasurg.2017.0552, PMID:28423155.

[3] Bennett IC, Gattas M, Teh BT. The genetic basis of breast cancer and its clinical implications. Aust N Z J Surg 1999;69(2):95–105. doi:10.1046/j.1440-1622.1999.01515.x, PMID:10030809.

[4] Liu R, Wang X, Chen GY, Dalerba P, Gurney A, Hoey T, *et al*. The prognostic role of a gene signature from tumorigenic breast-cancer cells. N Engl J Med 2007;356(3):217–226. doi:10.1056/NEJMoa063994, PMID:17229949.

[5] Easton DF. How many more breast cancer predisposition genes are there? Breast Cancer Res 1999;1(1):14–17. doi:10.1186/bcr6, PMID:11250676.

[6] Naeem M, Hayat M, Qamar SA, Mehmood T, Munir A, Ahmad G, *et al*. Risk factors, genetic mutations and prevention of breast cancer. Int J Biosci 2019;14(4):492–496. doi:10.12692/ijb/14.4.492-496.

[7] Verras GI, Mulita F, Tchabashvili L, Grypari IM, Sourouni S, Panagodimou E, *et al*. A rare case of invasive micropapillary carcinoma of the breast. Prz Menopauzalny 2022;21(1):73–80. doi:10.5114/pm.2022.113834, PMID:35388282.

[8] Verras GI, Tchabashvili L, Mulita F, Grypari IM, Sourouni S, Panagodimou E, *et al*. Micropapillary Breast Carcinoma: From Molecular Pathogenesis to Prognosis. Breast Cancer (Dove Med Press) 2022;14:41–61. doi:10.2147/BCTT.S346301, PMID:35310681.

[9] Flatley E, Ang D, Warrick A, Beadling C, Corless CL, Troxell ML. PIK3CA-AKT pathway mutations in micropapillary breast carcinoma. Hum Pathol 2013;44(7):1320–1327. doi:10.1016/j.humpath.2012.10.018, PMID:23352210.

[10] Kristensen VN, Borresen-Dale AL. Molecular epidemiology of breast cancer: genetic variation in steroid hormone metabolism. Mutat Res 2000;462(2-3):323–333. doi:10.1016/s1383-5742(00)00018-1, PMID:10767642.

[11] McKiernan E, McDermott EW, Evoy D, Crown J, Duffy MJ. The role of S100 genes in breast cancer progression. Tumour Biol 2011;32(3):441–450. doi:10.1007/s13277-010-0137-2, PMID:21153724.

[12] Bièche I, Lidereau R. Genetic alterations in breast cancer. Genes Chromosomes Cancer 1995;14(4):227–251. doi:10.1002/gcc.2870140402, PMID:8605112.

[13] Karami Fath M, Azargoonjahromi A, Kiani A, Jalalifar F, Osati P, Akbari Oryani M, *et al*. The role of epigenetic modifications in drug resistance and treatment of breast cancer. Cell Mol Biol Lett 2022;27(1):52. doi:10.1186/s11658-022-00344-6, PMID:35764927.

[14] Joshi S, Garlapati C, Aneja R. Epigenetic Determinants of Racial Disparity in Breast Cancer: Looking beyond Genetic Alterations. Cancers (Basel) 2022;14(8):1903. doi:10.3390/cancers14081903, PMID:35454810.

[15] Lunardi M, Al-Habbaa A, Abdelshafy M, Davey MG, Elkoumy A, Ganly S, *et al*. Genetic and RNA-related molecular markers of trastuzumab-chemotherapy-associated cardiotoxicity in HER2 positive breast cancer: a systematic review. BMC Cancer 2022;22(1):396. doi:10.1186/s12885-022-09437-z, PMID:35413811.

[16] Kazmi N, Robinson T, Zheng J, Kar S, Martin RM, Ridley AJ. Rho GTPase gene expression and breast cancer risk: a Mendelian randomization analysis. Sci Rep 2022;12(1):1463. doi:10.1038/s41598-022-05549-5, PMID:35087170.

[17] Zhou S, Huang YE, Liu H, Zhou X, Yuan M, Hou F, *et al*. Single-cell RNA-seq dissects the intratumoral heterogeneity of triple-negative breast cancer based on gene regulatory networks. Mol Ther Nucleic Acids 2021;23:682–690. doi:10.1016/j.omtn.2020.12.018,

PMID:33575114.
[18] Scherz A, Stoll S, Rothlisberger B, Rabaglio M. A New de novo BRCA1 Mutation in a Young Breast Cancer Patient: A Case Report. Appl Clin Genet 2023;16:83–87. doi:10.2147/TACG.S405120, PMID:37197323.
[19] Antoniou AC, Hardy R, Walker L, Evans DG, Shenton A, Eeles R, *et al*. Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. J Med Genet 2008;45(7):425–431. doi:10.1136/jmg.2007.056556, PMID:18413374.
[20] Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, *et al*. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer 2016;122(23):3673–3681. doi:10.1002/cncr.30248, PMID:27496084.
[21] Bubien V, Bonnet F, Brouste V, Hoppe S, Barouk-Simonet E, David A, *et al*. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet 2013;50(4):255–263. doi:10.1136/jmedgenet-2012-101339, PMID:23335809.
[22] Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, *et al*. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res 2006;12(10):3209–3215. doi:10.1158/1078-0432.CCR-06-0083, PMID:16707622.
[23] Benusiglio PR, Malka D, Rouleau E, De Pauw A, Buecher B, Noguès C, *et al*. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet 2013;50(7):486–489. doi:10.1136/jmedgenet-2012-101472, PMID:23709761.
[24] Uziel T, Lerenthal Y, Moyal L, Andegeko Y, Mittelman L, Shiloh Y. Requirement of the MRN complex for ATM activation by DNA damage. EMBO J 2003;22(20):5612–5621. doi:10.1093/emboj/cdg541, PMID:14532133.
[25] Barbano R, Copetti M, Perrone G, Pazienza V, Muscarella LA, Balsamo T, *et al*. High RAD51 mRNA expression characterize estrogen receptor-positive/progesteron receptor-negative breast cancer and is associated with patient's outcome. Int J Cancer 2011;129(3):536–545. doi:10.1002/ijc.25736, PMID:21064098.
[26] Adank MA, Jonker MA, Kluijt I, van Mil SE, Oldenburg RA, Mooi WJ, *et al*. CHEK2*1100delC homozygosity is associated with a high breast cancer risk in women. J Med Genet 2011;48(12):860–863. doi:10.1136/jmedgenet-2011-100380, PMID:22058428.
[27] Poumpouridou N, Kroupis C. Hereditary breast cancer: beyond BRCA genetic analysis; PALB2 emerges. Clin Chem Lab Med 2011;50(3):423–434. doi:10.1515/cclm-2011-0840, PMID:22505525.
[28] Vaidyanathan A, Kaklamani V. Understanding the Clinical Implications of Low Penetrant Genes and Breast Cancer Risk. Curr Treat Options Oncol 2021;22(10):85. doi:10.1007/s11864-021-00887-4, PMID:34424438.
[29] Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, *et al*. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007;39(7):870–874. doi:10.1038/ng2075, PMID:17529973.
[30] Smid M, Wang Y, Klijn JG, Sieuwerts AM, Zhang Y, Atkins D, *et al*. Genes associated with breast cancer metastatic to bone. J Clin Oncol 2006;24(15):2261–2267. doi:10.1200/JCO.2005.03.8802, PMID:16636340.
[31] Turnbull C, Rahman N. Genetic predisposition to breast cancer: past, present, and future. Annu Rev Genomics Hum Genet 2008;9:321–345. doi:10.1146/annurev.genom.9.081307.164339, PMID:18544032.
[32] Enderling H, Chaplain MA, Anderson AR, Vaidya JS. A mathematical model of breast cancer development, local treatment and recurrence. J Theor Biol 2007;246(2):245–259. doi:10.1016/j.jtbi.2006.12.010, PMID:17289081.
[33] Khoa Ta HD, Tang WC, Phan NN, Anuraga G, Hou SY, Chiao CC, *et al*. Analysis of LAGEs Family Gene Signature and Prognostic Relevance in Breast Cancer. Diagnostics (Basel) 2021;11(4):726. doi:10.3390/diagnostics11040726, PMID:33921749.