Review Paper:

Role of BRCA1 mutations in breast cancer susceptibility and treatment strategies

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Abstract

Breast cancer remains the most frequently diagnosed cancer, which is the leading cause of cancer-related mortality in women worldwide. Incidence rates vary across countries, with higher rates observed in regions with higher human development indices. Genetic mutations, particularly in BRCA1 and BRCA2 genes, play a significant role in breast cancer susceptibility, with implications for risk assessment and treatment decisions. Treatment options include surgery, chemotherapy and targeted therapies such as PARP inhibitors, with ongoing research focusing on improving outcomes and addressing drug resistance. Increased awareness, early detection and advancements in treatment have contributed to improvements in breast cancer outcomes in developed regions.

However, disparities in access to healthcare and resources persist, particularly in low and middle income countries. Addressing these disparities through organized screening programs, improved access to quality healthcare and continued research into personalized treatment approaches is crucial to reduce the global burden of breast cancer and improving outcomes for all patients. The review aims to provide a comprehensive overview of the epidemiology, risk factors, genetic mutations and treatment options associated with breast cancer, highlighting the global burden of the disease and its implications for public health.

Keywords: Breast Cancer, Epidemiology, Biomarkers, Treatment, Risk Assessment.

Introduction

Breast cancer (BC) still is the most common cause of cancer-related movements or fatality rates globally, with its epidemiology influenced by various factors including socio-economic status, access to healthcare and genetic predisposition. Understanding the dynamics of BC incidence, mortality rates and risk factors is crucial for effective cancer control and prevention strategies.[7] BC incidence rates vary significantly across regions, with higher rates observed in developed countries compared to low and medium-income nations. The disparity in incidence and mortality rates underscores the significance of addressing socio-economic determinants and implementing target interventions to reduce the burden of BC globally.[6]

The risk factors associated with BC include both non-modifiable factors such as gene mutations and modifiable factors like lifestyle choices and reproductive history. Genetic mutations play a significant role in BC etiology, with mutations in the BRCA gene being strongly related to increased BC risk and susceptibility to other cancers.[15] Advancements in genetic testing and molecular diagnostics have revolutionized BC management, enabling early identification of high-risk individuals and developing some personalized treatment strategies. Target therapy, such as PARP inhibitors, has emerged as a promising option for treating BC associated with specific genetic mutations, although challenges like drug resistance remain.[31]

Future directions in BC research aim to advances in genomics and precision medicine to improve patient outcomes and to reduce mortality rates. Efforts towards early detection, novel treatment modalities and equitable access to healthcare services are essential for mitigating the global impact of BC and improving survival rates. This review study provides an understanding and the role of BRCA1 mutations in breast cancer susceptibility and treatment strategies is vital for several reasons.

First, it facilitates the identification of individuals at higher risk of developing breast cancer, enabling targeted screening and early intervention to improve patient outcomes. Secondly, elucidating the mechanisms through which BRCA1 mutations contribute to breast cancer development informs the development of tailored treatment strategies, optimizing therapies for affected individuals. Additionally, exploring the challenges associated with current treatment approaches for BRCA1-mutated breast cancer guides future research efforts aimed at overcoming these obstacles, ultimately enhancing our understanding of breast cancer biology and improving risk assessment, early detection and treatment outcomes for affected individuals.

Epidemiology of the Breast Cancer

The incidence rates of breast cancer are calculated by the number of new individuals diagnosed with cancer as per the total number of individuals at risk of the disease over a specific period and population.[8] It is necessary to compare cancer incidences to have a clear knowledge of factors that have a relation with the disease. This comparison also makes

it easier to plan and to prioritize cancer control measures and evaluate cancer prevention programs. The Nation's development index, accessibility and uptake of breast cancer screening techniques such as mammography and self-examination are related to the prevalence of breast cancer.[36] Among the women diagnosed with cancer-related diseases, BC is the most common globally with more than two million new cases in 2020.[16] The Globocan data shows a positive and high correlation between the ASIR and HDI.[45]

Literature evidence revealed that age-standardized incidence rates (ASIR) of BC are very high in Nations, with the highest Human Development Index (HDI) with cases of 75 in 100,000. It is less in the middle as well as low Human Development Index countries (27.8 in 100 thousand and 36.1 in 100,000, respectively) by over one hundred (200%).[16] The human development index (HDI) depends on a Nation's achievements in three key areas: health, knowledge and life standard as prepared by WHO.[45] After being the most commonly diagnosed disease, BC ranks first among cancer-related fatalities in women globally, accounting for almost 700 thousand deaths at an age-adjusted rate of almost 14 in 100,000[5]. Despite the highest occurrence rate from developed countries, 60-63% of all deaths in 2020 were from Africa and Asia.[16] Also, women from lower and middle-income countries with BC barely survive, opposite happens with countries with higher incomes.[18] The 2020 figures show that the BC mortality to incidence ratio (MIR) was recorded at 0.30, indicating the 5-year survival rates worldwide.[16]

The new cases as well as the mortality rate of breast cancer have grown within the past three decades whereas the individual deaths from breast cancer quadrupled in 40 to 100 countries between 1990 and 2016 (e.g. Yemen, Libya, Saudiya). The incidence of the disease is two times more in sixty to hundred countries (e.g. Afghanistan, Philippines, Brazil, Argentina).[49] Current estimates suggest that by 2030, the fatality rate will hit almost 1 million per year globally with new incidences of about 2.7 million.[17] Because of the Westernized lifestyle (e.g. delay in pregnancy, reduced breastfeeding, no exercise, bad food and so on), improvement in cancer registration and improved cancer identification, it is expected that the prevalence of BC will continue to increase in lower and middle-income countries.[40]

Risk factors of breast cancer

List of breast cancer risk factors categorized into unchangeable elements and changeable factors are presented in the table 1. Unchangeable elements include factors like female sex, older age groups and family history while changeable factors include hormone replacement medication, exercise and alcohol consumption. The table provides a concise overview of the various factors that can influence an individual's risk of developing breast cancer, highlighting the importance of both genetic predisposition and lifestyle choices in disease prevention.[24] The increased hormone stimulation is one of the main causes linked to a high risk of breast cancer in women. Men's bodies contain negligible quantities of estrogen, but women's bodies contain breast cells that are highly sensitive to hormones (progesterone, estrogen in particular) and any changes in their equilibrium. A positive correlation has been found between the circulation of these hormones and a high risk of breast cancer.[24] One important factor that is strongly linked to an elevated risk of breast cancer, is a family history of the disease.[5,32,51]

Approximately 12-18% of patients with breast cancer reported having a first-degree relative with the disease.[10] An increased risk of ovarian cancer may also result from a family history of the disease, especially in cases where BRCA 2 and BRCA1 mutations are present.[15] About race and ethnicity, there are still many individuals who have been identified with breast cancer; the processes underlying these phenomena are still unclear.[20,56]

List of enzymes responsible for breast cancer

It has been revealed that several gene abnormalities affecting certain proteins have a high association with an increased risk of breast cancer. BRCA2 (chromosome 13) and BRCA1 (chromosome 17) are two prominent genes with strong penetrance that are mostly associated with an elevated risk of breast carcinogenesis.[50]

Table 1
Common risk factors associated with Breast Cancer and its classifications

S.N.	Unchangeable Elements	Changeable Factors
1	One female sex	Hormone replacement medication
2	Older age groups	Diethylstilbestrol
3	Family history	Exercise
4	Alterations in the genetic code	Being overweight or obese
5	Ethnicity/race	Use of alcohol
6	Being pregnant and nursing	Consuming tobacco
7	The menstrual cycle and the menopause	Inadequate dietary supplementation of vitamins
8	Breast tissue density	Overindulgence with artificial lighting
9	Prior incidence of BC	Processed feed consumption
10	Non-cancerous breast disorders	Chemical exposures
11	Prior radiation treatment	Other medications

The aforementioned genes primarily exhibit autosomal dominant inheritance when it comes to mutations; nevertheless, spontaneous mutations are also frequently documented. TP53, CDH1, PTEN and STK11 are also genes with high penetrant, associated with breast cancer.[9,11,12,23,48] The genes of such mutations not only have elevated risks of breast cancer, but they also have an increased risk of ovarian cancer. Several DNA repair genes such as (ATM, PALB2, BRIP1, or CHEK2), have been implicated in the induction of breast cancers and have been shown to interact with BRCA genes.

However, their penetrance is lower (moderate degree) than that of BRCA1 or BRCA2.[33,42,54,57] A recent study suggests that mutations in the XRCC2 gene also may have associations with a high risk of developing BC.[53]

Importance of the BRCA1 gene in the breast cancer

BRCA1 and BRCA2, are the most prevalent genes which are autosomal dominant and have a higher penetrance for breast cancer.[3] The genes are referred to be tumor suppressor genes (TSGs) because of the production of TSG proteins. One of the acrocentric chromosomes in men is chr17q which contains the BRCA1 gene and chr13q, which contains the BRCA2 gene.[3] Any mutations or alterations in these genes can increase the risks of breast cancer development. These genes generate TSG proteins and function as cell growth suppressors. The BRCA1 protein consists of 1863 amino acids and around 300 mutations that cause illness. 3418 amino acids are also present in the BRCA2 protein.[13]

The proteins, which are also known as anti-oncogenes, aid in DNA repair in damaged cells and guarantee the preservation of genetic material. If one of these genes is damaged, the resulting DNA damage is irreversible, resulting in additional cellular alterations and mutations that ultimately cause cancer.

Next, these TSG genes experience the condition known as Loss of Heterozygosity (LOH).[13] An individual who carries one problematic TSG allele who is heterozygous for this gene, experiences the phenomena. This person may develop LOH, which could result in the mutation of another healthy allele. The deteriorated TSG performance will make the cell more likely to grow a tumor, which will ultimately result in cancer, according to the Nadson two-hit theory.[13] The BRCA2 gene is known to predispose to breast cancer. The gene plays a crucial role in undamaged double-strand DNA break repair and transcriptional control. The BRCA2 gene guarantees the regulation of cell growth and DNA cell stability in healthy cells.[3,34]

Mutations involved in BRCA1

We have presented the list of mutations in the BRCA1 gene, along with their positions and mutation types in table 2. The mutations are categorized based on their exon locations and include various types such as deletions, substitutions and insertions. Each mutation is associated with a specific position in the BRCA1 gene, providing valuable information for researchers and clinicians studying the genetic basis of breast cancer susceptibility.

Understanding the spectrum of BRCA1 mutations is crucial for genetic testing, risk assessment and the development of targeted therapies for individuals with BRCA1-associated breast cancer.

Table 2
Nucleotide mutation mapping of BRCA 1 gene and it types

Exons	Mutations	Positions	Mutations type
2	185delAG[25]	185	Deletion
11	2201C >T[25]	2201	Substitution
11	2612C >T[25]	2612	Substitution
11	3279delC[25]	3279	Deletion
5	C181T >G[26]	181	Substitution
7	C560 + 2T >A[26]	560	Substitution
11	C2405_2406delTG[26]	2405-2406	Deletion
11	C3331_3334delCAAG[27]	3331-3334	Deletion
20	C5266dupC[27]	5266	Duplication
20	C5251C >T[27]	5251	Substitution
11	3587del T[27]	3587	Deletion
9-12	C5482_4185+7del[28]	5482	Deletion
11	C2296-2297delAG[28]	2296	Deletion
11	C2433delC[28]	2433	Deletion
11	C3598C >T[28]	3598	Substitution
11	C4327C >T[28]	4327	Substitution
18	C5123C >T[28]	5123	Substitution
20	5382insC[28]	5382	Insertion
6	300T>G[28]	3000	Substitution
18	5396+1G>T[28]	5396	Substitution

The increased risk of prostate and ovary cancer development in males and females respectively with a 60% to 80% chance of causing breast cancers in women is related to BRCA1 gene mutations.[3] The mutations in the genes are linked with faster mitotic rate and high lymphatic penetration.[35] Carriers of the BRCA 1 gene mutation have a high chance of acquiring other cancers in addition to the risk of BC development.[14,21] Almost two thousand mutations are discovered in the BRCA 1 gene, where novel mutations are highly uncommon. Negative mutations, missense, tiny insertion, small deletions, untimely termination of transcriptions and splice mutation, are the most prevalent mutations.[29,37,41,54] The nonsense, frameshift and splicing mutations that cause the protein shortening are the majority causes of breast cancer.[3,36]

Role of BRCA1 in other diseases: The two most prevalent genes, BRCA1 and BRCA2, are high penetrance in the forms of ovarian and breast cancer and are autosomal dominant.[3] Additionally, for ovarian cancer, Wilms tumor, melanoma, glioblastoma, medulloblastoma, pancreatic cancer, Fanconi anemia, cancer of the prostate, fallopian tube cancer, biliary cancer and melanoma are common.[2,34]

Surgical interventions: Breast tumors with and without BRCA1 or BRCA2 mutations have been shown to differ in several investigations. In the case of women with BRCA mutations, for example, there is an increased risk of developing a secondary cancer, which can occur in the ipsilateral breast or the contralateral breast. According to research, women who carry the BRCA1/2 mutation and undergo a bilateral hysterectomy, are recommended to have this procedure rather than a unilateral one to reduce the risk of dying from breast cancer.[38,43]

Chemotherapy

The chemotherapeutic drugs known as taxanes stabilize microtubules and prevent cell division, which causes apoptosis. The two taxanes that are mostly used to treat breast cancer are paclitaxel and docetaxel, which received medical approval in 1993 and 1995 respectively. A recent meta-analysis study revealed that taxane is less toxic and both generate comparable clinical results. Taxane-based therapy may be a preferable choice for advanced breast cancer patients than the anthracycline-taxane combination.[57] Direct binding of the platinum agents to DNA results in DNA/platinum adducts, causing double-strand breaks and interstrand DNA crosslinks. Only 22% of patients receiving combinatorial therapy with doxorubicin, cyclophosphamide and occasionally fluorouracil, had a complete and pathological response (PCR).[8]

The inhibitors of PARP enzymes also known as poly ADP-ribose polymerases are crucial to DNA damage repair processes. The initiation of the DNA damage response is facilitated by PARP activation, specifically through PARP-1 to PARP-3. To entice DNA repair complexes to assemble at damaged locations, PARP synthesized an ADP-ribose polymer.[30] PARP inhibitors prevent DNA damage from being repaired, which causes unstable chromosome cell cycle arrest and consequent apoptosis. This ultimately results in the continued existence of DNA lesions that would typically be repaired by homology recombination.

The PARP inhibitors use a mechanism known as "synthetic lethality" to target tumors with BRCA1 or BRCA2 gene defects. DNA breaks on one strand (S SBs) are increased by PARP inhibitors and become irreversible, lethal DNA double-strand breaks during replication. PARP inhibitors increase the number of DNA breaks on one strand (SSBs) which in BRCA1/2 deficient cells, undergo irreversible harmful double-strand breaks in DNA (DSBs) during replication. PARP medications help to treat patients who carry germline BRCA mutations, according to clinical research. Furthermore, bearers of non-BRCA mutations may potentially benefit from PARP inhibitors.[31]

Targeted therapy

Lists most commonly used drugs targeting BRCA1, along with their clinical status and inhibitory concentrations (IC_{50}) are arranged in the table 3. The drugs include PARP inhibitors like olaparib and talazoparib, as well as other small molecular inhibitors such as ataluren and cyclophosphamide monohydrate which are mainly used during the treatment of breast cancer patients injured by BRCA1. The table provides an overview of the pharmacological agents currently available or under investigation for the treatment of BRCA1-mutated breast cancer. Understanding the mechanisms of action and clinical status of these inhibitors is essential for optimizing treatment strategies and improving outcomes for patients with BRCA1-associated breast cancer.

These medications are used in the treatments of breast cancer, particularly in those with BRCA1 gene mutations. They are classified as poly (ADP-ribose) polymerase (PARP) inhibitors. The method of action involves taking advantage of synthetic lethality, which occurs when cancer cells with BRCA mutations die because of inability to repair the damage to their DNA that PARP inhibition has produced.[9] If genetic breast cancer runs in the family, one or more of the following characteristics may be taken into account when making a clinical diagnosis: The following conditions have been identified: i) early-onset breast cancer, ii) the presence of two breast cancers, either primary or related other organs cancer, present in one person; iii) populations at risk (Ashkenazi Jews); iv) an individual in family who has a known mutation on a gene related to breast cancer.[39]

By evaluating probable genomic reorganization in the genes BRCA1 or BRCA2, a molecular genetic test is utilized to determine BRCA mutations.[39] The NCCN has revised its recommendations for genetic testing, counseling, risk assessment and genetic/familial high-risk assessment. To decrease the risk of breast cancer in people with BRCA1 or

BRCA2 mutations, preventive mastectomy, monitoring and chemoprevention are among the primary prevention techniques.[55]

An adjuvant tamoxifen treatment reduced the occurrence of contralateral breast cancer in 1504 individuals with inherited BRCA1 or BRCA2 mutations by 50%, according to a recent study.[26] For patients with postmenopausal, the choice of treatment with tamoxifen medication is currently based on the stage of the disease, the chance of recurrence, age, or personal preference. According to ASCO guidelines, it is recommended to make transition to an estrogen inhibitor at some time during anti-estrogen therapy. According to research, premenopausal women who get tamoxifen medication for ten years, may experience a lower chance of breast cancer returns.[52]

Limitations of existing drugs

The drugs associated with BRCA1 and its side effects include symptoms provided in the table 4. This table provides a concise summary of the potential adverse effects associated with each drug which is an important information for clinicians and patients to consider when making treatment decisions. It highlights the need for balancing the potential benefits of these drugs with the risks of adverse reactions in breast cancer management.

BRCA1 mutation carriers are a subpopulation of hormone-negative malignancies that are less sensitive to taxane and chemotherapy than patients whose cancers are not hormone-negative. In contrast, both inherited and sporadic cases in the subset of hormone-positive tumors exhibit comparable susceptibilities to taxane treatment.[27] Additionally, a study revealed that in inherited BRCA1 linked to breast cancer, neoadjuvant chemotherapy increases the response to platinum drugs and reduces the response to taxanes.[8] The use of PARP inhibitors in the adjuvant, neoadjuvant and metastasis settings for the management of ovarian, BRCA mutated breast cancer,[22] and other malignancies is the subject of numerous clinical investigations.[15] Despite the optimism around this new type of medication, Sanofi-Aventis's most advanced PARP inhibitor Iniparib failed clinical studies in 2011.

Table 3
Small molecule inhibitors targeting BRCA 1 and its clinical status

S.N.	Drug Name	Clinical status	IC_{50}
1	Olaparib[41]	Approved	5 nM
2	Ataluren[42]	Approved	0.1uM
3	PF-04217903[43]	experimental	4.8nM
4	Lumacaftor[44]	Approved	0.1uM
5	Cyclophosphamide Monohydrate[45]	Approved	-
6	Alectinib[46]	Approved	1.6nM
7	Talazoparib[47]	Approved	0.57nM
8	Proflavine Hemisulfate[48]	Approved	-
9	Crenolanib[1,49]	experimental	
10	Niraparib[50]	Approved	-
11	Dacomitinib[11,51]	Approved	6nM
12	Olmutinib[52]	experimental	3nM

Table 4
Adverse effect of existing drugs of BRCA1 in Breast Cancer

S.N.	DRUG	SIDE EFFECTS
1	Tamoxifen	Hot flashes, Vaginal discharge, nausea
2	Anastrozole	Joint pain, hot flashes, fatique,
3	Letrozole	Joint pain, hot flashes, fatique,
4	Exemestane	Joint pain, hot flashes, fatique,
5	Palbociclib	Hair loss, nausea, fatigue
6	Ribociclib	Diarrhea, nausea, fatigue
7	Abemaciclib	Diarrhea, nausea, fatigue
8	Trastuzumab	Diarrhea, nausea, chills, fever
9	Pertuzumab	Diarrhea, nausea, fatigue
10	Lapatinib	Diarrhea, nausea, rash
11	Olaparib	Nausea, vomiting, diarrhea, headache, loss of appetite and increased risk of infection.
12	Rucaparib	Blood counts vary
13	Niraparib	Constipation, blood count varies
14	Talazopari	Nausea, vomiting, diarrhea, Anemia, loss of appetite, low white blood count.

In clinical studies conducted in 2011, Sanofi-Aventis's most advanced PARP inhibitor, Iniparib, failed to extend life in phase III in patients with triple-negative breast cancer, despite the optimism around this new class of medications. The study from 2013 indicated that the appearance of a subsequent BRCA2 mutation, was correlated with clinical findings of PARPs blocking drug resistance, which was linked to the failure. The synthetic lethal strategy will likely be jeopardized by this mutation, which is anticipated to restore the function of wild-type proteins.[4]

Future direction

Regarding alternatives for prevention and therapy, the BRCA mutation status can offer a clear and helpful insight. BRCA mutation carriers may be able to diagnose or to prevent cancer at an early stage if there is a high likelihood of successful therapy through the use of enough care and surveillance. The environments for customized (precise) treatment options will probably shift due to advancements in bioinformatics and the declining cost of genome sequencing.

This will affect individuals with uncommon genetic mutations that were not previously thought of, as well as those who carry BRCA mutations. Finding the complex abnormality that makes each patient's cancer highly susceptible to a given treatment is the ultimate goal, as is matching each patient with the clinical trials or available medicines that will be most helpful to them.

Conclusion

This study offers a comprehensive update on the current understanding of breast cancer, covering its epidemiology, risk factors, classification, prognostic markers and treatment options. In developed regions, the mortality rate from breast cancer has significantly declined due to heightened awareness, early detection and improved therapies. However, lower-income areas continue to bear a disproportionate burden of breast cancer mortality due to limited resources and inadequate access to quality healthcare.

To reduce breast cancer-related deaths, enhance early detection and alleviate the global burden of the disease, it is crucial to implement well-managed screening programs, to establish breast cancer databases and expand access to mammography screening in less developed regions.

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