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# A Review on Breast Cancer: A Global Risk Factor and Preventive Measures

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## Abstract

Breast cancer is a matter of global concern due to its widespread occurrence worldwide. The concerning rise in breast cancer cases highlights the need to address the disease on multiple fronts. This requires a comprehensive approach, starting with rigorous cancer screening or cancer registry, and extending to effective methods of diagnosis and treatment. Breast cancer is characterized by significant variability in both its appearance and molecular characteristics, necessitating diverse treatment regimens tailored to specific molecular subtypes. Consequently, breast cancer patients with different subtypes can expect distinct clinical outcomes. The heterogeneity of breast cancer underscores the importance of advanced molecular testing, which enables timely diagnosis and improved chances of survival. Emerging fields like artificial intelligence and liquid biopsy hold promise in unraveling the complexities of breast cancer and determining the most appropriate treatment strategies. In this review, we have explored various risk factors and cutting-edge technologies available for diagnosing breast cancer, with the aim of addressing the challenges associated with this disease and enhancing breast cancer management.

**Keywords:** Breast cancer, Epidemiology, Incidence, Risk factors

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## Incidence and Epidemiology of Breast Cancer

Breast cancer is a significant health concern for women due to its high rates of mortality and morbidity. Even with the implementation of adjuvant chemotherapy, the five-year survival rate for metastatic breast cancer is below 30%. According to recent data from the International Agency for Research on Cancer, collected across 185 countries in the GLOBOCAN 2020 report, there were 2.3 million new cases (11.7% of all cancer cases) of breast cancer, with a mortality rate of 6.9% [1-3]. The incidence of breast cancer is more prevalent in high-income countries (571 cases per 100,000 individuals) compared to low-income countries (95 cases per 10,000 individuals), a trend that is associated with globalization. Breast cancer is widely recognized as a heterogeneous disease with over 100 different biological subtypes, each exhibiting unique molecular profiles and clinicopathological features. In addition to the various histological subtypes, gene expression profiling has further categorized breast cancer into distinct molecular subtypes, including receptor-positive subtypes (Luminal A, Luminal B, Normal-like, and HER-2 positive) and receptor-negative subtypes (Triple-negative breast cancer or Basal-like) [4].

Lehmann et al. have also identified different groups within the triple-negative breast cancer subtypes based on the expression of specific genes, such as Basal-like-1, Basal-like-2, Immunomodulatory, Mesenchymal, Mesenchymal Stem Cell-like, and Luminal Androgen [5, 6]. These subtypes of breast cancer demonstrate distinct histopathological and clinical behaviors and are associated with different age groups and ethnicities. For instance, triple-negative breast cancer and HER-2 positive subtypes are more prevalent in premenopausal and younger women particularly among African American and Asian women [7]. These subtypes are characterized by a higher potential for metastasis and a greater likelihood of relapse. In developed countries, modified lifestyle, delayed age for marriage, late first child, late-night work schedule, and hormonal replacement therapy are the major risk factors for breast cancer development. In developing nations, the primary factors contributing to the elevated incidence and mortality rates of breast cancer are inadequate awareness or knowledge regarding the disease, inadequate screening initiatives, delayed diagnosis, and insufficient medical resources.

Various treatment options exist for breast cancer, including surgical procedures, chemotherapy, radiotherapy, endotherapy, and immunotherapy [8-11]. Despite the existence of these treatment modalities, breast cancer incidence and mortality rates remain high. To address this issue, multiple omics studies have revealed both intra- and inter-tumor heterogeneity in breast cancer, which is the primary cause of treatment relapse or resistance. Furthermore, scientific researchers and clinicians are continuously enhancing existing knowledge and technologies to

investigate tumor heterogeneity in breast cancer. Improvements or advancements in sequencing tools, such as next-generation sequencing, single-cell sequencing, spatial gene expression profiling, and bioinformatics support, are providing significant assistance in understanding tumor heterogeneity [12, 13]. Moreover, several authorized agencies are conducting screening programs targeting women at high risk of breast cancer to reduce incidence rates. Despite the availability of these resources, the number of new breast cancer cases continues to rise. This is primarily due to inaccurate information and a lack of proper utilization of these resources. Additionally, the ongoing COVID-19 pandemic has resulted in the closure of healthcare systems and screening programs, leading to delays in diagnosis and treatment availability, as well as an increase in advanced-stage diagnoses and mortality rates. This review article aims to provide an overview of the current status of breast cancer morbidity and mortality, the major risk factors involved, and possible strategies for breast cancer risk prevention [14].

## Risk Factors for Breast Cancer

### Genetic risk factors

As a result of the genes, genetic risk factors are inherited from one parent to another. These risk factors cannot be changed since they are inherent in your DNA from birth. Environmental and lifestyle risk factors, on the other hand, are avoidable risk factors that can usually be managed by an individual [15]. The risk factors can be reduced through changes to your environment or lifestyle. Genetic risk factors, however, cannot be changed which include.

#### Gender

Women are nearly 100 times more likely to develop breast cancer than men.

#### Age

Invasive cancer is diagnosed in two out of three women over the age of 55.

#### Race

Caucasian women are more likely to be diagnosed with breast cancer than women of other races.

#### Menstrual and reproductive history

A woman's risk of breast cancer can be increased by early menstruation (before the age of 12), late menopause (after the age of 55), having your first child at an older age, or never having given birth [16].

#### Dense breast tissue

It can be more difficult for you to detect lumps when you have dense breast tissue. Several states have enacted laws requiring physicians to disclose to women that their mammogram indicates they have dense breasts. In order to be aware of the risks associated with dense breasts, you should consult your physician to determine if you have dense breasts.

#### Certain genome changes

Genetic tests can determine whether you have a higher risk of breast cancer if certain genes, such as BRCA1 (Breast cancer gene 1) and BRCA2 (Breast cancer gene 2), are mutated. If you have a family history of breast cancer, you may want to consider undergoing a genetic test. It is possible for individuals with such gene mutations to pass the mutation on to their children as well.

#### Family history and genetic factors

If one of your close relatives has been diagnosed with breast or ovarian cancer, you are more likely to develop breast cancer in the future, especially if their diagnosis occurred before the age of 50.

#### Personal health history

The risk of developing breast cancer in the other breast is increased if you have previously had breast cancer in one breast. If you have previously been diagnosed with abnormal breast cells such as atypical hyperplasia, lobular carcinoma *in situ* or ductal carcinoma *in situ*, your risk increases [17-20].

### Environmental and lifestyle risk factors

#### Drinking alcohol

Alcohol consumption can increase your risk for breast cancer. As you consume more alcohol, your risk increases.

#### Radiation to the chest

Breast cancer can increase your risk if you receive radiation therapy before the age of 30. Despite the fact that radiation therapy is often an unavoidable treatment for certain illnesses, it is still considered an environment or lifestyle risk factor since it is not a trait inherited by a person [21].

#### Lack of physical activity

Exercise or moving your body for even 20 minutes a day can help lower the risk of breast cancer. A sedentary lifestyle accompanied by little physical activity can increase your risk of breast cancer [22].

#### Combined hormone replacement therapy

In addition to increasing the risk of breast cancer and making it more likely that the cancer will be detected at an earlier stage, combined hormone replacement therapy can also result in an increased risk of breast cancer. You should discuss the benefits and risks of combined hormone replacement therapy with your physician.

#### Poor diet

Consuming 3.5 to 5 cups of fruit and vegetables a day can help lower your risk for breast cancer, as a diet high in saturated fat and lacking in fruits and vegetables may increase your risk.

#### Being overweight or obese

Obesity, characterized by a high waist-to-hip ratio, poses a significant risk for breast cancer in postmenopausal women and is also associated with unfavorable disease outcomes in women of all age groups. In the United States (US), approximately 18% of premenopausal women exhibit an elevated body mass index, placing them at a heightened risk for the development of breast cancer. It has been observed that postmenopausal women with a body mass index of ≥ 5.0 and an abdominal circumference of ≥ 90 cm are more susceptible to breast cancer. This susceptibility arises from the activity and buildup of polycyclic aromatic hydrocarbons in breast adipose tissue. Within breast tissue, a higher intake of alcohol is metabolized by the alcohol dehydrogenase enzyme into acetaldehyde. The accumulation of acetaldehyde can bind to proteins and DNA, thereby interfering with the antioxidative defense system, DNA synthesis, and repair mechanisms, through the down-regulation of BRCA1. Hormonal contraception formulations typically contain lower doses of estrogen; however, prolonged use can also elevate the risk of breast cancer in women [23].

## Epidemiology

In 2018, an estimated 6.8 million women worldwide were diagnosed with breast cancer. However, the data recorded in cancer registries lacks comprehensive information on the number of women who have experienced metastatic spread and have subsequently become cancer-free. Currently, only the incidence or mortality rates are being documented in these registries [24]. The incidence of breast cancer varies greatly across the globe due to disparities in education levels, economic status, environmental conditions, dietary habits, lifestyle factors, and cultural practices. It is projected that globalization, and a growing economy will further contribute to an increase in breast cancer incidence in developing countries (64% to 95%) and developed countries (32% to 56%) by 2040. In urban areas of India, the highest incidence of breast cancer was reported among women aged 40 - 49, while in rural areas, it was observed among women aged 65 - 69. A study conducted on the population of northern India revealed that 26% of breast cancer patients were younger than 35 years old. Additionally, differences in dietary patterns, such as the consumption of tobacco (smoked vs smokeless), alcohol (spirits vs wines), and nonvegetarian diet (high vs low red meat intake), also contribute to the variation in breast cancer incidence [25, 26].

### Breast cancer burden globally

Breast cancer is the most prevalent form of cancer among women in the US, excluding skin cancers. It accounts for approximately 30% (or 1 in 3) of all newly diagnosed female cancers on an annual basis. According to the estimations provided by the American Cancer Society, the US is projected to see the following statistics for breast cancer in 2023:

- Approximately 297,790 new cases of invasive breast cancer will be detected in women.
- Around 55,720 new cases of ductal carcinoma in situ (DCIS) will be diagnosed.
- Approximately 43,700 women will succumb to breast cancer.

Breast cancer predominantly affects middle-aged and older women. The median age at the time of diagnosis is 62, indicating that half of the women diagnosed with breast cancer are 62 years of age or younger. There is a minimal occurrence of breast cancer among women under the age of 45 [27].

According to the American Cancer Society, the global burden of cancer is projected to reach 28.4 million cases by the year 2040, representing an increase of approximately 47% compared to the burden in 2020. Older women are known to have a higher incidence of breast cancer. In 2018, there were 645,000 cases of breast cancer reported among premenopausal women, compared to 1.4 million cases among postmenopausal women. Similarly, the respective numbers of deaths were 130,000 and 490,000. It has been observed that countries with a high human development index have the highest incidence of breast cancer among both premenopausal (30.6/100,000) and postmenopausal (253.6/100,000) women, while countries with low and medium human development index have the lowest rates of premenopausal (8.5/100,000) and postmenopausal (53.3/100,000) mortality [28]. The inadequacy in accessing early diagnosis and effective treatment remains a critical factor contributing to higher breast cancer mortality rates in developing countries.

Accordingly, the overall risk of a woman in the US developing breast cancer at some point in her life is approximately 13% (Figure 1).

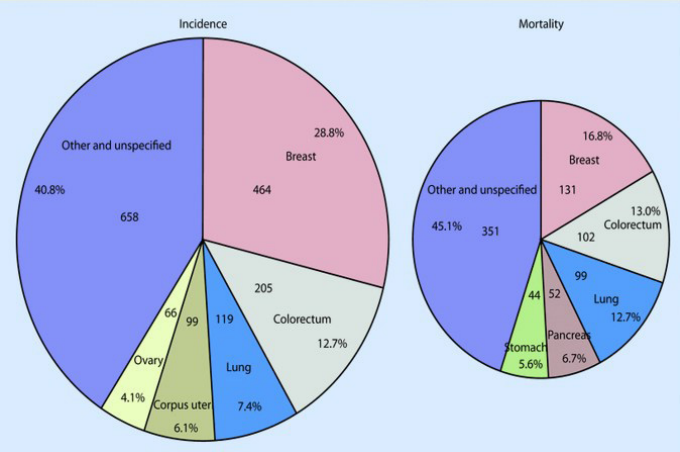


**Figure 1:** Number of new cases and deaths per 100,00 women in the United States (Source: https://oncohemakey.com/breast-cancer-epidemiology) Data from the Global Burden of Cancer Study (GLOBOCAN 2020).

Therefore, she has a 1 in 8 chance of developing breast cancer. However, she also has a 7 in 8 chance of never developing breast cancer.

Breast cancer ranks as the second most common cause of cancer-related mortality among women, second only to lung cancer. The probability of a woman succumbing to breast cancer stands at approximately 1 in 39, equivalent to approximately 2.5%. The mortality rates associated with breast cancer have exhibited a consistent downward trend since 1989, with an overall reduction of 43% up until 2020. This decline is widely attributed to the early detection of breast cancer through screening initiatives, heightened awareness, and advancements in treatment modalities. Nonetheless, the pace of this decline has experienced a slight deceleration in recent years [29-31].

Racial and ethnic variations in breast cancer can be observed. For example, the median age at diagnosis for Black women is slightly younger, at 60 years old, compared to White women, who are diagnosed at 63 years old. Notably, Black women have the highest mortality rate from breast cancer. This disparity is believed to be partially attributed to the fact that approximately 1 in 5 Black women with breast cancer have triple-negative breast cancer, a higher proportion than any other racial or ethnic group. Additionally, Black women face a higher likelihood of developing breast cancer before the age of 40 compared to White women. At all ages, Black women are more susceptible to succumbing to breast cancer than individuals of any other race or ethnic background. In contrast, White, Asian, and Pacific Islander women have a greater probability of being diagnosed with localized breast cancer compared to individuals from Black, Hispanic, American Indian, and Alaska Native communities. Furthermore, Asian and Pacific Islander women exhibit the lowest mortality rate from breast cancer, while American Indian and Alaska Native women have the lowest incidence rates of developing the disease [32].

### Breast cancer burden in India

The incidence in India has witnessed a significant increase of nearly 50% between the years 1965 and 1985 [3]. The estimated number of new cases reported in India in 2016 was 118,000 (with a 95% uncertainty interval ranging from 107,000 to 130,000), out of which 98.1% were females. Additionally, the number of prevalent cases was recorded at 526,000 (with a range of 474,000 to 574,000). Over the course of the past 26 years, the age-standardized incidence rate of breast cancer among females has risen by 39.1% (with a 95% uncertainty interval ranging from 5.1 to 85.5), spanning the period from 1990 to 2016. This increase was

observed across all states in the country. According to the GLOBOCAN data for the year 2020, breast cancer accounted for 13.5% (178,361) of all cancer cases in India. Furthermore, it represented 10.6% (90,408) of all deaths, resulting in a cumulative risk of 2.81 [33-35].

Current trends indicate that there is a higher incidence of disease among younger Indian women compared to the Western countries. The National Cancer Registry Program conducted an analysis of cancer registry data from 1988 to 2013 to examine changes in cancer incidence. All population-based cancer registries have shown a significant upward trend in breast cancer. In 1990, cervical cancer was the most common type of cancer in India, followed by breast cancer in the registries of Bengaluru (23.0% vs 15.9%), Bhopal (23.2% vs 21.4%), Chennai (28.9% vs 17.7%), and Delhi (21.6% vs 20.3%). In Mumbai, breast cancer was the leading site of cancer (24.1% vs 16.0%). However, by the years 2000 - 2003, the scenario had changed, and breast cancer had become the leading site of cancer in all the registries except in the rural registry of Barshi (16.9% vs 36.8%). In the case of breast cancer, a significant increasing trend was observed in the registries of Bhopal, Chennai, and Delhi [36].

With regards to the 5-year overall survival, a study has reported that it stands at 95% for stage I patients, 92% for stage II patients, 70% for stage III patients, and only 21% for stage IV patients. The survival rate of breast cancer patients in India is comparatively low when compared to Western countries due to factors such as an earlier age at onset, the presentation of the disease at a late stage, delays in initiating definitive management, and inadequate or fragmented treatment. According to the World Cancer Report 2020, the most effective approach for controlling breast cancer is early detection and prompt treatment. A systematic review conducted in 2018, which analyzed 20 studies, found that the costs of breast cancer treatment increased with a higher stage of cancer at the time of diagnosis. As a result, early diagnosis of breast cancer can help reduce treatment costs [37].

In a recent study conducted in Mumbai, primary health workers conducted clinical breast examinations every two years to significantly decrease breast cancer stage at diagnosis, resulting in a non-significant 15% reduction in breast cancer mortality overall (but a significant 30% reduction in mortality among women over 50 years of age) [38]. The sensitivity of mammography varies from 64% to 90% [16] and the specificity is 82% to 93%. As a consequence of the density of Indian breasts, and a lack of adequate mammography machines and trained staff, digital mammography can result in false positives and overdiagnosis. However, it remains a relatively expensive procedure. Due to these factors, routine mammography screening at large scale is not considered an ideal option for a country in transition like India [39].

In general, ultrasound has an overall sensitivity of 53% to 67% and a specificity of 89% to 99% [40]. This method is especially useful for younger women (aged 40 to 49 years old). However, the requirement that trained professionals perform and interpret ultrasound is a major obstacle to overcome. In spite of the fact that breast self-examination is not considered a reliable early detection method for breast cancer, it can serve as an integral component of educating a woman regarding her normal breast health if used diligently and skillfully.

By utilizing genomics to understand India-specific differences, we may be able to identify women who have high cancer risks, allowing us to conduct targeted screenings to reduce the risk. There is an urgent need to identify Indian-specific genetic/epigenetic biomarkers that can be used to facilitate early detection at the screening stage [41].

## Approaches to Control Breast Cancer

An extensive breast cancer information program is of utmost importance, to create awareness among the public regarding risk factors and incidence of breast cancer. To reduce the burden of breast cancer incidence and mortality, it is essential to conduct screening programs and perform diagnostic tests in order to detect breast cancer early.

### Next generation sequencing

During the past four decades or more, a range of molecular profiling technologies, such as immunohistochemistry, gene expression microarrays, and germline DNA sequencing, have significantly influenced the medical treatment of individuals diagnosed with breast cancer. While the classification of breast cancers based on molecular subtypes has been extensively researched and integrated into clinical care protocols, the genomic characteristics of advanced-stage breast cancers are a developing area of exploration enabled by next-generation sequencing (NGS) technologies. A recent study conducted an analysis of 10 tumor-normal matched specimens from over 10,000 patients with advanced cancer, including 1,234 breast cancer patients. The study utilized the institutional Memorial Sloan Kettering-IMPACT NGS assay to compile a comprehensive catalog of somatic mutations in late-stage tumors. Subsequently, another study integrated the genetic data from the aforementioned 1,234 breast cancer patients with clinical and treatment information to identify genomic alterations responsible for resistance to hormonal therapy. It has also been reported that 41 patients with advanced breast cancer profiled using the FoundationOne CDx panel were analyzed with the NGS test results from the Cancer Center Dachau in Germany. These studies have advanced the knowledge of breast cancer progression and drug resistance; however, a larger study involving real-world data will be necessary to understand how NGS will benefit patients with breast cancer in practice [42, 43].

An unprecedented achievement in molecular biology has been achieved by the advancement of traditional sequencing technologies with extraordinary depth read counts and the analysis of entire genomes in one experiment. The NGS technology has revolutionized genomic research by enabling massive parallel and deep sequencing in a single experiment. In a single set of experiments, next generation sequencing provides complete genome information through the use of a multigene panel. By using this high throughput technique, it is possible to detect gene variants, gene alterations, point mutations, gene fusions, and copy number variations. In addition to contributing to the development of patient-specific therapies, advanced sequencing techniques have been widely accepted throughout the world for diagnosing breast cancer [43-46]. The popularity of NGS in diagnostics can be attributed to several distinct advantages, including its ultrahigh throughput, scalability, and speed. The NGS technologies such as the reversible dye terminator method by Illumina, semiconductor ion proton by ThermoFisher Scientific, SMRT PacBio, and Nanopore by Oxford, enable the identification of a wide range of genetic aberrations (such as SNP, CNV, Indel, translocation, and gene expression), protein expressions, and epigenetic alterations with exceptional accuracy and sensitivity [47]. As well as quantifying the copy number of cellular RNAs in various tissues, RNA sequencing may also reveal novel or splice site mRNA variants. Furthermore, NGS is used to study epigenomic modifications across the genome, including histone modification, DNA methylation, and DNA-protein interaction, as well as genome wide epigenomic modifications.

Furthermore, Oxford Nanopore Technologies has developed a simple experimental process for analyzing DNA strands directly as they

pass through a thin membrane with a tiny pore suspended inside. In order for the device to function, the current must change as the nucleotides pass through a pore consisting of protein sets, which is based on the combination of G, A, T, and C nucleotides [48-50]. It has the advantage of reading label-free, ultralong (104 to 106 bases) sequences, generating high-throughput data despite low material use, rapid processing, and real-time results display. It is widely acknowledged that phenotypic and molecular heterogeneity in tumors is a major cause of therapy failure and resistance. To improve the survival rate of breast cancer patients, it is necessary to understand and decode tumor heterogeneity. The template switch method offers advantages over bulk sequencing data in terms of decoding tumor heterogeneity in this context. As a result of spatially resolved high-resolution transcriptomics, it was possible to decipher the heterogeneity of tumor cells within intact tissue sections. Sequential Fluorescence *In-Situ* Hybridization, Fluorescent *In-Situ* Sequencing, GeoMx, Slide-seq, STARmap, High-Definition Spatial Transcriptomics, and Multiplexed Error-Robust Fluorescence *In-Situ* Hybridization are spatial molecular imaging technologies that can be used to examine thousands of RNAs and proteins from single cells in intact tissues with subcellular resolution [51-54].

Researchers can visualize and quantify target protein and gene expression in tissue slices using spatial molecular imaging, which combines high-plex profiling with high-resolution imaging. In addition, there are many online repository databases containing information on the three omics related to breast cancer. As a result of the genetic, transcriptomic, protein expression, and epigenetic information obtained from a significant number of breast cancer patients, databases such as The Cancer Genome Atlas, Gene Expression Omnibus, and Molecular Taxonomy of Breast Cancer International Consortium provide substantial amounts of information. Additionally, these databases contain clinicopathological characteristics of breast cancer patients, which can be used for meta-analysis [55].

## Genetic testing

After reviewing your personal and family history, your doctor or genetic counselor may request a genetic test to check for harmful gene mutations. These tests may include:

- A single mutation test looks for a mutation in a specific area of one gene.
- A single gene test analyzes an entire gene to see if there are any mutations.
- A panel test looks for mutations in multiple genes.

The most common germline mutations associated with early-onset breast cancer, triple-negative breast cancer, bilateral breast cancer, and a family history of breast cancer are BRCA1 and BRCA2. These mutations account for up to 30% of inheritable breast cancers. Non-BRCA mutations that are less common have also been identified and have contributed to hereditary breast cancer syndromes. Despite the establishment of genetic testing for BRCA mutations, indications, and interpretations of genetic testing in non-BRCA mutations have not been established. Additionally, genetic testing costs are highly variable, depending on laboratory costs, insurance coverage, and individual risk factors [56-57].

Several systematic reviews have been conducted that summarize published literature concerning genetic testing for BRCA1 and BRCA2 for breast and ovarian cancer. These genes are extremely large genes. Since the cloning of BRCA1 and BRCA2, more than 1,000 mutations have been identified. Based on the available literature, there is no conclusive evidence to indicate superior performance of one genetic test over another [58]. In order to conduct a comprehensive mutation screening, it is necessary to employ multiple methods. Variations in populations result in variations in mutations, hence the choice of mutation analysis often depends on the specific population or subpopulations. Individuals belonging to families with identified mutations can be more conveniently tested for those specific mutations. Populations in which specific BRCA mutations are concentrated due to a shared ancestor are referred to as founder populations.

The estimation of cancer risk in family history risk groups involves assessing the prevalence and penetrance of mutations associated with breast and ovarian cancer. The prevalence of these mutations can vary depending on the geographic and ethnic background of the population [59]. Limited data exist regarding the prevalence of clinically significant BRCA1 or BRCA2 mutations in the general population. However, models suggest that the prevalence is approximately 1 in 397 individuals. Systematic reviews have revealed that a substantial proportion (up to 36%) of women with breast cancer who carry these mutations do not have a family history of breast or ovarian cancer.

Several clinically significant mutations of BRCA1 and BRCA2 have been identified repeatedly in families, such as the four founder mutations that are most prevalent in the Norwegian population.

It is estimated that women with these inherited gene mutations will incur a cumulative lifetime risk of 65 % for BRCA1 and 45 % for BRCA2, and these cancers often develop at a younger age. It has been estimated that the ovarian cancer penetrance for women carrying BRCA1 mutations is 39 % and is slightly lower, 11 %, for women carrying BRCA2 mutations [60].

In Norwegian women carrying one of the four BRCA1 founder mutations, the cumulative lifetime risk of breast or ovarian cancer is approximately 58 percent (51 - 66%).

The effective medical management of mutation carriers includes increased surveillance, chemoprevention, and prophylactic surgery. In short-term cohort studies, prophylactic surgery was associated with reduced breast and ovarian cancer risks. However, it remains unclear how to manage women who undergo prophylactic surgery optimally [61].

Generally, international guidelines recommend testing for mutations only when a person's personal or family history suggests inherited cancer susceptibility, the test can be properly interpreted, and the results will assist in the treatment process. Prior to testing, genetic counselling is recommended.

## Molecular testing

In addition to genetic testing for genetic and genomic variations, molecular testing for breast cancer management has become an integral part of managing breast cancer. It is imperative to conduct genetic testing to determine if a hereditary cancer syndrome is present in patients with a family history of breast cancer, other tumors, bilateral breast cancer, or early-onset breast cancer. All patients diagnosed with advanced breast cancer are now required to undergo hereditary cancer testing due to the availability of PARP inhibitors, which are selectively active in patients with BRCA1/2-associated breast cancers. In the management of advanced breast cancer, tumor genomic profiling has become increasingly important. It is currently the standard of care for many types of malignancies. Targetable mutations in advanced breast cancer include PIK3CA, HER2, and rare instances of mismatch deficiency or other targets for tyrosine kinase inhibitors [62-64].

The development of methods for sequencing cell-free DNA should facilitate the broader and more convenient implementation of tumor genomic testing. Transcriptome-based expression signatures have become the standard of care in the management of early-stage estrogen receptor–positive breast cancers. These assays offer prognostic significance in the context of adjuvant endocrine therapy and are predictive of the benefits derived from adjuvant chemotherapy. For instance, PAM50 (Prediction Analysis of Microarray 50) is an US Food and Drug Administration (FDA)-approved multigene kit that provides better insights into breast tumors and prognostication in ER-positive, HER-2-negative, lymph node-negative, and > 5cm tumor size breast cancers. In order to test breast tumor samples for distant recurrence within 10 years of diagnosis, microarray-based PAM 50 tests 50 genes. PAM50 scores indicate a fairly high risk of metastases if the scores are high [65-67]. As a result of these developments, molecular testing has become a part of the clinical management of the majority of breast cancer patients today. In hormone receptor-positive and node-negative breast cancer patients, the Breast Cancer Index predicts relapse of cancer within five to ten years of diagnosis. Because molecular diagnostic assays are capable of estimating the risk of metastasis, tumor recurrence, and therapy response, they are an integral part of breast cancer management. Based on the outcome of the test, the clinician can determine how long to delay hormonal therapy in a patient [68].

## Liquid biopsy

Liquid biopsies have shown promising results in breast cancer research, particularly in the areas of treatment response monitoring and disease progression or relapse prediction. With further investigation and advancements in tumor-derived material isolation technologies, liquid biopsies may have a more substantial impact on breast cancer clinics. Recently, the USFDA also authorized the use of the Therascreen PIK3CA RGQ polymerase chain reaction assay as a companion diagnostic tool for detecting PIK3CA mutations in breast cancer, for both tissue and liquid biopsies. This highlights the increasing importance of liquid biopsy in breast cancer management. However, its potential in other aspects of breast cancer remains to be clearly defined [69].

A liquid biopsy is conducted by using body fluids such as blood, urine, saliva, stools, or cerebrospinal fluid as a source of tumor-derived materials, such as tumor DNA, RNA, intact tumor cells, or extracellular vesicles, liquid biopsy is conducted. Compared to traditional tumor biopsy, it is a relatively noninvasive investigation modality due to the fact that the materials are obtained through methods such as blood drawing or urine collection. In addition, it is purported to offer the advantage of overcoming tumor heterogeneity through sampling the entire genomic landscape of the tumor present within a patient, as well as the capability of repeating the test over time, allowing for longitudinal monitoring of the tumor and its response to antitumor treatments. There might also exist potential in the early detection of cancers, prognostication, and prediction of response to treatment. In recent times, the advancement of remarkably sensitive assays capable of detecting the frequently minuscule quantity of tumor-derived material in bodily fluids has rendered liquid biopsy a feasible substitute for traditional tumor biopsies, with its significance in the treatment of lung cancer being the primary illustration. In this examination, we explore the progression of liquid biopsies in breast cancer up until now and conclude with a few of our insights for the future [70].

## Artificial intelligence

Incorporating artificial intelligence (AI) into screening methods, such as the examination of biopsy slides, has significantly reduced mortality rates for breast cancer. As a result of this increased interest in this area over the last few years, the field appears to have a very bright future. It involves computer vision, lesion detection, or pattern recognition in order to carry out procedures which were previously performed by experts, as well as systematic reporting (diagnosis) for the classification of lesions in accordance with Breast Imaging Reporting and Data System. Additionally, imaging biomarkers are extracted for the purpose of modeling therapy responses based on predictability and prognosis. Machine learning and deep learning are essential components of AI that are necessary for breast cancer imaging. Machine learning is utilized to store a vast dataset, which is subsequently employed to train predictive models and interpret generalizations. Deep learning, the most recent branch of machine learning, operates by establishing a network of artificial neural networks capable of classifying and recognizing images. In the domain of breast cancer screening, AI primarily encompasses object detection (segmentation) and the classification of tumors as either benign or malignant [71-74].

A radiomic technique used in AI systems is known as radiomics. It extracts quantitative features from images. It is usually accomplished using pattern recognition algorithms that recognize images and provide as their outcome a set of numbers representing a quantitative feature of the image under consideration. The underlying principle of radiomics is that extracted features represent various biological and molecular processes. As part of machine learning, computational algorithms are employed to extract image features by employing radiomics, in order to help understand disease outcomes. Radiomics employs two types of machine learning: unsupervised and supervised. Unsupervised machine learning classifies information without relying on any preexisting data or obtaining data from the image itself. In supervised machine learning, AI is trained using existing data archives as a basis. As with supervised machine learning, deep learning uses a multi-neural layer or network to process an image, reducing it to a set of numbers that represent features [75].

Within the realm of breast cancer treatment, the utilization of AI for early detection is achieved through the analysis of data procured from radiomics and biopsy slides. This endeavor is bolstered by a global initiative to develop machine learning algorithms that enhance the comprehension of mammograms, thereby mitigating the occurrence of false positives [76]. Furthermore, AI has significantly heightened the probability of identifying metastatic breast cancer within comprehensive whole slide images of lymph node biopsies. Due to the inherent variation in individuals' risk factors and predispositions, AI algorithms operate in a distinctive manner across diverse populations.

Mammography is widely regarded as the most popular method for breast cancer screening. It involves obtaining a high-resolution image, which is subsequently utilized without any restrictions on age or body size. Full-field digital mammography systems encompass both input (raw images) and output (post-processing) formats. The AI is employed to analyze the images and detect various aspects such as breast masses, mass segmentation, breast density, and cancer risk assessment. The identification of breast masses is particularly crucial in computer-aided diagnosis, as they are frequently encountered in breast cancer patients. Mammography can reveal two types of calcifications, namely microcalcifications and macrocalcifications, which appear as small spots. Presently, computer-aided diagnosis systems are capable of detecting microcalcifications [77, 78].

Accurate breast mass segmentation, which involves the precise demarcation of tumor boundaries, directly impacts the diagnostic process. Fuzzy contours are utilized to automatically segment breast masses from the mammogram. However, due to inherent irregulari-

ties that vary from person to person, breast segmentation can be challenging. Nevertheless, the implementation of AI greatly enhances the accuracy of segmentation, consequently improving patient prognosis. Breast density assessment is conducted using two-dimensional mammograms. Furthermore, breast cancer risk assessment relies on evaluating various risk factors such as age, family history, reproductive factors (e.g., menarche, menopause, age during the first pregnancy, parity), estrogen levels, and individual lifestyle choices.

Two decades ago, computer-aided detection was introduced as a component of screening mammography. Numerous studies were conducted to assess the efficacy of single reading by radiologists compared to double reading by computer-aided detection. Although no definitive advantage was observed for either approach, the combination of both methods has reportedly yielded a higher success rate. Moreover, studies have demonstrated the considerable potential of AI-based computer-aided detection in achieving high sensitivity [34]. This technology can expedite the reading process in digital breast tomosynthesis (DBT) and serve as a preliminary screening tool for excluding low-risk mammograms. While computer-aided detection has predominantly been used as an alternative opinion or decision support in patient care, it is imperative that it undergoes rigorous evaluation and demonstrates its efficiency prior to integration. Ensuring the stability of the results obtained over time is also of paramount importance [79, 80].

Using immunotherapy as a treatment method, we are able to take advantage of patients' immune system responses. Artificial intelligence algorithms make it easy to identify neoantigens, however more research and investment are required. It is also possible to use AI to predict immunotherapy responses. As a result of studies linking immunotherapy response to radiomic characteristics, uniform trends have been revealed across cancer types and anatomical locations.

## Approaches to Implement

### Screening program

In 2021, 2.7 million new cases of breast cancer will be diagnosed worldwide, according to the most recent available data. Based on local cancer registry data for 2019, it appears that breast cancer incidence is probably higher in the Kingdom of Saudi Arabia than in other countries where most studies are conducted.

In 2021, 372,000 women in the US were estimated to have been diagnosed with breast cancer, and 60,000 women were estimated to have died from it. The median age at which women are diagnosed with breast cancer is 68 years. Breast cancer death rates are alarmingly high, especially when compared with all cancer mortality rates. It is therefore essential that breast cancer screening programs are endorsed in order to facilitate early detection and prompt treatment.

Breast cancer screening with mammography is the most common and widely used method of detecting breast cancer worldwide. Additionally, breast self-examinations, clinical breast examinations, digital breast tomosynthesis (DBT), ultrasound (USG), magnetic resonance imaging (MRI), and identification of certain genetic oncogene mutations are some of the other methods used in breast cancer screening around the world [81].

While breast self-examination is performed by the female herself to identify lumps or other abnormalities in the breast, clinical breast examination is performed by a physician or healthcare professional. There is no consensus among experts regarding the widespread use of these two methods in breast screening as the potential benefits to reduce mortality are not convincing.

### Mammography

Mammography entails the visualization of breast tissue through the utilization of low dose X-rays, serving as either a screening or diagnostic tool. It is primarily advised for elderly women between the ages of 50 and 75 [9]. Mammography is typically not employed as a routine screening method for females under 40 years old, primarily due to the presence of dense glandular tissue and the potential risk of ionizing radiation. Despite its cost-effectiveness, it remains the most commonly utilized screening technique for breast cancer in women over the age of 40.

The purpose of DBT is similar to that of digital mammography. Three-dimensional images are obtained by combining thin cross-sectional images with conventional X-rays. It is more effective for women with dense glandular tissue. A DBT screening test has been approved for breast cancer by the FDA since 2011 [82].

#### Merits of mammography

In addition to early detection of breast cancer, mammography provides lower stage benefits in terms of decreased morbidity, since the cancer can be treated with less toxic treatments, such as breast conservation surgery, and frequently without chemotherapy. When breast cancer is detected early at a lower stage and treated early, there has been a better 5-year survival rate, which has been proven. 99% of localized breast cancer patients survive 5 years, 84% of regional cancer patients survive 5 years, and 23% survive metastatic breast cancer.

An analysis of 11 trials with 13 years of follow-up reported reduced mortality rates, with an estimated 20% decrease in mortality from breast cancer in women invited for screening, along with substantial reductions in death from breast cancer. In different age groups, mammography can reduce the death rate from breast cancer by 3% in women in their 40s and 49s, 8% in women in their 50s and 60s, 21% in women in their 60s and 70s, and 13% in women in their 70s and 74s [83-86].

#### Demerits of mammography

It is important to note that screening mammography has the following disadvantages. It is possible to incur serious harm if precancerous lesions, such as ductal carcinoma *in situ*, are detected early, which may lead to repeated biopsies and unnecessary treatment, but it may not progress to invasive breast cancer for the remainder of the life span.

Among females aged 40 - 49 years, the false-positive biopsy recommendation rate after screening mammography is 7 - 9.4%, while among women 50 - 59 years, the rate is 4.8 - 6.4%. This is based on a cumulative study published in February 2016 by the USPSTF [87].

There are also disadvantages to screening mammography, including the detection of noninvasive cancer that does not result in death or threaten the life of women without screening. False positive results may not only result in psychological and behavioral changes but may also result in additional visits and additional costs. Furthermore, false positives may also result in anxiety and additional costs.

### USG

Women with dense glandular tissue are typically screened with USG, especially those with mammographic microcalcifications and clinically suspicious breast lumps [88].

#### Merits of USG

A significant advantage of USG is its ability to obtain images of the

breast from virtually any direction. It is noninvasive, does not involve radiation exposure, and can be performed on younger women with dense breasts and during pregnancy. This is an economical and patient friendly procedure. As a result, it can be a useful tool for identifying cystic disease as well as needle biopsy of solid tissue lesions and fine needle aspiration cytology.

### Demerits of USG

In addition to lacking spatial resolution and fine detail, USG cannot detect most calcium deposits in breast cancers. USG is not capable of documenting the amount of breast tissue imaged. USG will not usually be able to identify lesions larger than 1 cm. Due to its high operator dependence, it requires skilled sonologists, high-quality examinations, and modern equipment [89].

### MRI

As MRI is not a cost-effective method of screening breast cancer, and there are not sufficient facilities to conduct large population-based screening programs, it is not widely used for screening. Moreover, there are no promising results supporting its use as a breast cancer screening tool throughout the world.

### Merits of MRI

The major advantages of MRI are manifold. Firstly, MRI can provide comprehensive imaging of the entire breast in all planes, without any risk of ionizing radiation. Additionally, it is capable of generating three-dimensional images and detecting multifocal lesions, occult lesions, and residual malignancy. Moreover, MRI exhibits exceptional spatial resolution, enabling accurate measurement of lesion size. In the context of breast lesions, MRI demonstrates a remarkably high negative predictive value. Furthermore, it can effectively image lymph nodes and metastasis, thereby aiding in the staging of breast cancer. Notably, MRI is particularly adept at identifying breast cancer at its earlier stages, especially among women with BRCA 1 and BRCA 2 positive mutations. Lastly, MRI consistently produces excellent results when evaluating implants [90-94].

### Demerits of MRI

In addition to its limited availability, MRI is 10 times more expensive, requires contrast enhancement, multiple images, and is difficult to interpret, making it unsuitable for widespread use as a breast cancer screening modality. It has also been reported that false positive results can be as high as 30% in benign lesions, such as carcinoma in situ variable enhancement.

The identification of the BRCA oncogene has indicated an increased likelihood of breast cancer occurrence in individuals with a previous history of breast cancer, a family history of breast cancer, and ovarian cancer. Nevertheless, the presence of positive mutations or a family history of breast cancer does not guarantee the development of breast cancer in patients detected with the BRCA oncogene. The widespread implementation of breast cancer screening programs has been limited due to concerns of overdiagnosis, overtreatment, and the resulting psychosocial impact on the personalities of unaffected women. Consequently, recent restrictions on breast cancer screening have been adopted globally [95].

### Cancer registry

The purpose of a cancer registry is to collect, store, and manage information on cancer patients.

Cancer registries play a critical role in cancer surveillance, which is crucial for reducing the cancer burden. Cancer surveillance data are also useful in cancer research and for planning and evaluating cancer prevention and control measures.

Using data on cancer surveillance, health officials, researchers, and others can answer questions such as, "Are more or fewer people developing colorectal cancer this year than last?" or "What are the most likely groups of people to develop skin cancer?".

The National Cancer Institute utilizes the Surveillance, Epidemiology, and End Results (SEER) Program to support cancer surveillance activities. It represents an authoritative source of information on cancer incidence and survival in the US. The SEER Program presently gathers and publishes cancer incidence and survival data from population-based cancer registries encompassing approximately 48 percent of the US population [96-98]. The SEER Program is a component of the National Cancer Institute utilizes Surveillance Research Program, which provides nationwide leadership in the field of cancer surveillance, as well as analytical tools and methodological expertise in the collection, analysis, interpretation, and dissemination of dependable population-based statistics [99]. Furthermore, the SEER program facilitates various forms of cancer-related research by assisting patients in connecting with clinical trials that assess the efficacy of novel treatments, supporting studies that collaborate with patients to address specific inquiries regarding their cancer care and outcomes, and providing backing for other categories of epidemiologic studies [100].

## Molecular Technologies - Types of Biomarkers for Diagnosis, Prognosis, Drug Resistance, and Therapeutic Implications

It has been discovered that there are different types of biomarkers that are helpful in diagnosing, prognosing, and assessing drug resistance as well as therapeutic implications. These biomarkers may assist in resolving the issue of drug resistance in the treatment of breast cancer. There is a strong link between DNA methylation patterns and carcinogenesis, as over 90% of breast cancer patients showed methylated promoters for retinoic acid receptors-2 and adenomatous polyposis coli [101-103]. According to Yang et al., in a BeadChip DNA study of human methylation, hypomethylation of S100 calcium-binding protein P and hyaluronoglucosaminidase 2 and S100 calcium-binding proteins were found to be associated with adolescent breast cancer patients [199, 200]. It has been established over the years that noncoding RNAs such as circular RNAs and microRNAs (miRNAs) have promising diagnostic and prognostic properties for breast cancer. For all stages of breast cancer, miR-221, miR-21, and miR-145 have demonstrated greater diagnostic susceptibility than CEA or CA 15-3 in the blood serum and plasma of breast cancer patients. A study by Iorio and colleagues in 2005 identified deregulated miRNAs in breast cancer patients (mir-125b, mir-145, mir-21, and mir-155). A study by Blenkiron and colleagues in 2007 identified 133 miRNAs in human breast tissue and breast tumor tissue [104-106]. Circular RNA molecules represent approximately one eighth of the human genome. Circular RNA molecules are very stable in all kinds of body fluids due to their circular structure and nonterminal ends. As described in Lu et al., HBSA circ 103110, HBSA circ104689, and HBSA circ104821 were upregulated [AUC values of 0.63 (0.52 - 0.74), 0.61 (0.50 - 0.73), and 0.60 (0.49 - 0.71), respectively] in breast cancer patients, but downregulated HBSA circ006054, HBSA circ100219, and HBSA circ406697 [AUC values of 0.71, 0.78, and 0.68, respectively [107]. According to the published literature, all of these biomarkers possess clinical potential and should be explored further to

determine their clinical utility.

## Conclusion

The gathered epidemiological data on breast cancer thus far has aimed to assess the severity of the disease. Urgent attention is required to develop sensitive, specific, easily accessible, and cost-effective diagnostic and therapeutic approaches in order to decrease the incidence and prevalence of breast cancer. The present review articles describe various strategies being utilized across different continents. However, the use of diagnostic or predictive biomarkers may vary in different regions due to their ethnic-based variations. The effectiveness of preventive and screening programs is also influenced by the economic conditions of the country. Therefore, it is crucial to validate the biomarkers effectively in order to determine region-specific cutoff values. Additionally, a substantial amount of data on all three omics has been accumulated at the research level only. To effectively integrate this information into clinical practice, large-scale validation is necessary. Addressing all these issues would contribute to reducing the incidence and prevalence of breast cancer.

## Future Perspective

Studies have found that each breast cancer patient has distinct genetic, transcriptional, and epigenetic characteristics. Different studies have explored breast cancer heterogeneity by using genetic (mutations) and genomic (gene expression) data. Classification of Luminal A breast cancer subtype into different groups by analyzing copy number and mutational landscape data from multiple studies (mixed, copy number high, chromosome 8 associated, copy number quiet, and 1q/16q). Breast cancer is characterized by heterogeneity at both phenotypic and molecular levels, reducing treatment efficacy and, therefore, clinical outcomes. Genome profiling can be used to examine the molecular heterogeneity in an individual patient, allowing for individualized treatment. Next generation technologies need to be improved in order to provide higher accuracy, greater sensitivity, and lower costs to patients, so they are available to all. Although, the discovery of DNA, RNA, protein- and epigenetic-based diagnosis, and therapeutic biomarkers would improve the understanding of breast cancer, the non-reproducibility of these markers between patients within and outside of the continental US limits their application. In order to prevent breast cancer, awareness of the disease is the most effective prevention method. A variety of breast cancer awareness and screening programs should be developed at different levels. Women should be aware of their breasts and instructed about self-screening and breast cancer. Women at high risk for breast cancer should take extra precautionary measures, such as counseling and clinical consultation.

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## Conflict of Interest

None.

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