Chapter

Breast Health and Preventive Screening

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Abstract

Breast health and its importance in every stage of a woman's life is discussed from adolescence, across the life span, and addressing the aging process. The importance of self-breast exams, clinical breast exam, and screening mammograms play an integral part of ensuring early detection of breast cancer. The risk factors, genetic mutations, and how breast cancer is triggered is discussed. The advancements in screening recommendations, genetic testing, and treatments is explored and what innovative approaches are being taken to prevent, treat, and cure breast cancer.

Keywords: mammary glands, mammogram, breast cancer screening, BRCA1 & 2 gene, breast cancer, next-generation sequencing, MammaPrint, adjuvant therapy

1. Introduction

The breasts for male and female are similar through childhood where they both have undeveloped breast tissue. This similarity changes for females between ages 8–10 years of age when the breasts begin to develop prior to menarche (start of menses) and continues through puberty [1]. Menarche usually begins around age 12 when the Tanner stage has reached stage 3 or 4. The breasts begin to respond to hormonal changes of increased estrogen during puberty where other changes become evident as well such as pubic hair and hair growth in the axillary region occurs. The breast development process is one that can be described through tanner stages 1–5 in progression until the female breasts are fully developed and rounded with the nipples protruding (see **Table 1**) [1].

Males have breasts that remain basic in function throughout life that is not as complex as the female breast, nor does it have the capability to produce breast milk to breast feed an infant. The obvious breast differences between the two genders provides a platform for discussing the breast anatomy of the female, the response to hormones, and its function(s) [1].

2. Breast anatomy

The breast is comprised of mammary ducts, lobules, fatty tissue, blood vessels, connective tissue, areola, nipples, and lymph nodes. The picture below provides a visual of what a fully developed breast looks like (**Figure 1**) [4].

Female breast stage	Breast changes
Stage 1	Nipple raised in pre-teen stage
Stage 2	Nipple buds begin to develop/widen more as do the breasts begin to grow slightly raised/mound
Stage 3	Breasts continue to enlarge/grow with more glandular tissue development and is flush with the nipple
Stage 4	Breasts are more rounded into a mound and a secondary areolar mound is present
Stage 5	Maturity of the breast is achieved, often with the areola darker and flush with the breast mound

Table 1.
Tanner stages 1–5: [2].

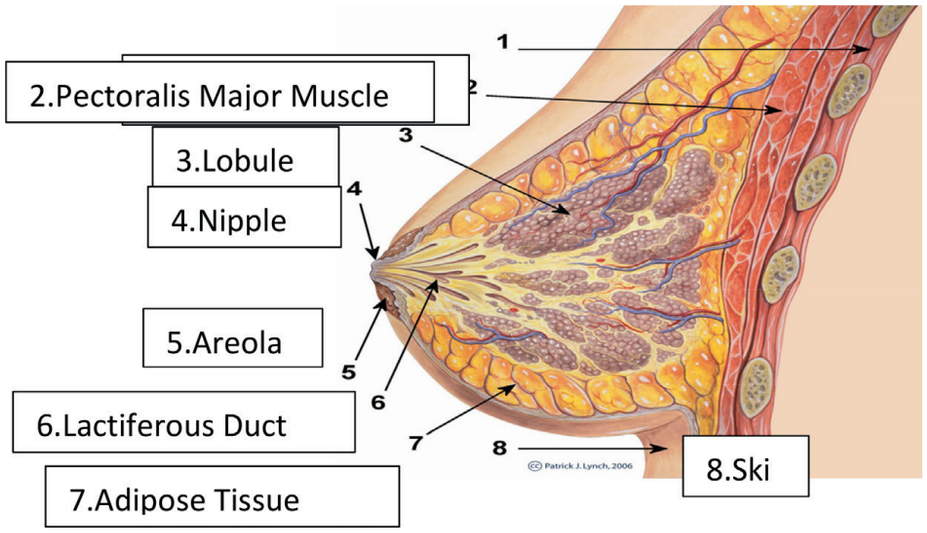

Figure 1.
Breast anatomy Normal Scheme [3].

Breast tissue is derived from lobules and mammary ducts, stroma that is inter and intra lobular in origin, and squamous and epithelial cells. The initial development of lobules (type 1) occurs during puberty. Through the adolescent years, the development of the female breasts continues into early adulthood where type 2 (alveolar maturity) and type-3 lobular mammogenesis (increased breast tissue growth) is triggered by pregnancy [5]. The hormonal changes of higher levels of progesterone and the production of chorionic gonadotropin prepare the breasts to enlarge, lobules to develop further and be able to secrete colostrum and breast milk (lactogenesis) [5].

The breasts' lymph nodes play a significant role in keeping the body healthy by producing lymph fluid and white blood cells called lymphocytes that protect the body from infection and other disease processes. If cancer is present in a specific part of the body, it can shed cancer cells that are either collected through the blood lymph nodes or circulated through the blood vessels. Since the lymph nodes function as a filter, most cancerous cells will remain trapped and not spread to other areas of the body. If cancer cells do escape the lymph node(s), then it can begin to grow in other areas of the body. This process of cancer cells originating in one location and then having a secondary location is known as metastasis (**Figure 2**) [7].

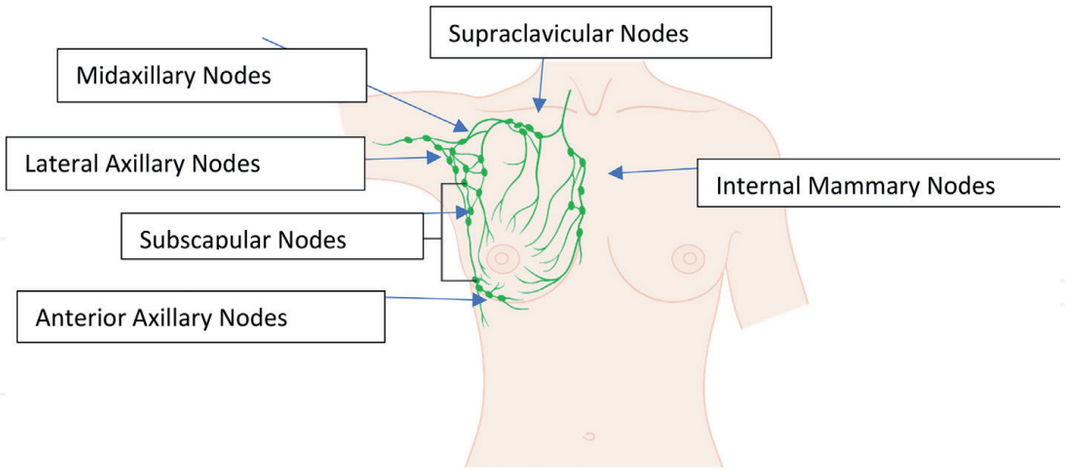

Figure 2.
Lymph nodes of the breast [6].

2.1 Breast feeding

Once the mother delivers her infant, there is a cascade of hormonal processes that occur. The anterior and posterior pituitary gland play a role in hormone stimulation and milk production. Prolactin is regulated by the anterior pituitary and this hormone is released when the infant is breast feeding which triggers the need to produce more milk [5]. Oxytocin, produced in the hypothalamus, is regulated by the posterior pituitary gland for its release. This hormone is released when areolar stimulation from suckling occurs which in turn allows the milk to be released during breast feeding, also known as the "letdown reflex." Oxytocin has additional benefits that relieve stress and assist in the mother's relaxed and calm demeanor [5]. One added benefit of oxytocin is believed to assist in a mother bonding with her infant. A prospective study in Australia conducted over a 15-year period suggests that there is a correlation between non-breast-feeding mothers and those that breast fed for a very brief period and a lack of bonding which may contribute to maternal maltreatment in the form of neglect. This neglect was inversely correlated to the time spent breast feeding, thus the more months an infant was breast fed, the less likely neglect occurred, due to a stronger bonding relationship developed because of oxytocin as mentioned previously. This study's review also found that those who did not breast feed or breast fed for a short period of time had a higher rate of post-partum depression [8].

Milk production or reduction of milk production is regulated by a feedback inhibitor that is based on the intramammary pressure built up from either milk released or milk accumulated and not released. If the pressure is increased from too much milk built up, then milk production will decrease until the excess pressure is relieved and thus a cyclic process occurs to ensure that milk is produced after a feeding to prepare for the next feeding [5].

Breast feeding is a personal choice for many; however, there are multiple benefits to breast feeding an infant. The mother's immunity is passed onto the infant, the composition of the mother's milk provides digesting benefits along with all the nutrients that the infant will need to develop properly. Breast milk helps to protect the infant from obesity and chronic illnesses [5]. There have been several studies that provide data that breast feeding provides long-term benefits to the mother. There are many conditions that are inversely related to breast feeding that lowers the disease process associated with the following conditions: hypertension,

hyperlipidemia, diabetes mellites, metabolic syndrome, cardiovascular disease, cerebral vascular accident, breast cancer, ovarian cancer, endometrial cancer, and rheumatoid arthritis [8].

2.2 Mature breast changes aged 40 and older

Aging breasts often begin to change during perimenopause and after achieving menopause when hormone levels, especially estrogen and progesterone, begin to decrease, and the breasts begin to sag and become less dense. This process occurs as women enter their 40s and 50s. In review, the breasts developed during puberty due to an increase in estrogen and progesterone, so it makes sense that the decline in these same hormones will cause the decline in breast tissue density and fullness. Subsequently, breast cancer is also associated with aging and 80% of all new breast cancers are diagnosed when the woman is in her 50s or older [9].

Multiple risk factors correlate to a higher risk of breast cancer with age being the primary risk factor to consider for both men and women [10]. Other risk factors include familial history of breast cancer and/or history of BRCA gene mutation confirmation, a personal history of breast cancer, exposure to high radiation levels, excessive hormone therapy, age of menarche, Ashkenazi Jewish lineage, and age of first delivery [9]. Other relative risk factors include: higher socioeconomic status, never having had children, alcohol use, did not breast feed, reached menopause after age 55, postmenopausal obesity, and pregnancy after age 30 [1]. These risk factors coupled with age related mammary changes make breast tissue more susceptible to tumor-related mutation in conjunction with lower tumor suppressor effectiveness/response, and damage from exposure to environmental components that may also contribute to changes in breast tissue [11].

Changes in the aging breast from exposure to environmental, hereditary, hormonal, and multiple other risk factors provides insight into the alterations in the cellular and genetic expression of "hormone-sensing and secretory-alveolar lineage markers" as well as inflammatory processes that may contribute to genetic expression mutations [11, 12]. When you combine inflammation with declining bodily function, older age, weight gain (harbors estrogen), and macrophage infiltrative processes together, then you have a recipe for a tumor microenvironment (TME). TMEs are comprised of tumor mediators and tumor cells that regulate the proliferation and metastasis of breast cancer, and it is a good indicator of breast cancer prognosis, especially triple negative breast cancer [12]. Macrophage infiltration prompts a domino effect that activates myeloid-epithelial-reproductive tyrosine kinase (MER TK), which in the right microenvironment, promotes the mutated genetic expression instead of repairing the original genetic expression [13]. The negative affect of MER TK activation for aberrant expression includes hindering cell apoptosis and the expedited activation of metastasis that is resistant to cancer treatments [13].

3. Breast cancer screening and recommendations

Breast cancer screening recommendations from the United States Preventive Services Task Force (USPSTF) provide guidance for women aged 40 and over on breast cancer screening frequency. Since 2016, the recommendation has been for women aged 40–49 to speak with their physician and determine whether every other year screening mammograms is appropriate for them. However, the

recommendations are currently being updated to suggest that women aged 40–49 begin screening mammograms every other year. It is recommended that women aged 50–74 maintain routine screening mammograms every other year [14] . The American Cancer Society (ACS) has slightly different recommendations with women aged 40–45 choosing to have annual screening mammograms and women aged 45–54 with annual screening mammograms, and women aged 55 and older to have screening mammograms every other year [9]. The American College of Obstetricians and Gynecologists (ACOG) recommends screening mammograms every 1–2 years for women aged 40–75 [9].

The USPTF and the ACS do not recommend clinical breast examinations and/or self-breast examinations; however, ACOG recommends clinical breast examinations every 1–3 years but no self-breast examinations [9]. These recommendations provide guidance, but to give patients the tools to make informed decisions about their healthcare and body is imperative. Teaching your patients and/or significant other how to examine their breasts once a month empowers self-care, self-awareness, and early detection. Why is this important? Abnormalities identified through patients performing breast self-exams account for 40% of all breast cancer diagnosis [15]. When a patient comes into a clinic and states that they have a lump in their breast, the first question that will be asked of the patient encompasses two parts: (1) "How long has this lump been there?" and (2) "How much has it grown since you found it?" If the patient cannot answer either of these two important questions, then there will be great anxiety from the patient as to what is not known and/or what to expect going forward. Being able to answer these questions helps to gauge the aggressiveness of the lump/mass. Once a history and clinical breast exam is conducted, then a diagnostic mammogram or US should be ordered, depending on their age [16].

With the increase in transgender women on the rise, combined with estrogen hormone therapy, and androgen hormone blocking therapies, it is important to mention that breast cancer is increasing among this population. The reasons vary, but could be contributed to: continuous use of exogenous hormone therapies, the patient's inability to feel a lump due to possible breast augmentation, lack of education with the patient on how to do a breast self-examination, lack of knowledge from primary care providers on how to care for transgender patients, and/or a current lack of screening recommendations for this diverse population [10]. This evolving group of patients will need to begin to assume the risk that ciswomen have and begin to think in these terms to assess their genetic risk of breast cancer and screen accordingly [10].

The rate of breast cancer among men is much lower than it is form women, however, there are still similarities in risk factors such as age, familial history of breast cancer or BRCA1 or 2 mutation, obesity, and radiation exposure. Other risk factors that women do not have is as follows: testicular disorders, Klinefelter syndrome, and gynecomastia (enlarged breasts for men) [10]. Men have a rate of breast cancer incidence of 1.2 per 100,000 men and this accounts for only 1% of all breast cancer diagnosis between 2015 and 2019. Unfortunately, with so little known about male breast cancer, the signs are often overlooked until it is diagnosed at a later cancer stage, usually regional or distant, which makes it harder to treat and correlates to a lower survival rate compared to women [10] . Black men have a higher rate of breast cancer overall as well as sub-types compared to other ethnicities [10]. There is still a lot of work to do to inform men about their risk of breast cancer and when to get checked, but with the help of primary care providers, this can be a conversation that occurs during an annual well check visit.

3.1 Breast cancer risk assessment tool

The Breast Cancer Risk Assessment Tool (BCRAT) is a tool that determines the risk one has over a 5-year and lifetime risk based on their individualized risk factors to provide a risk score prediction that is valid among all ethnicities [17]. This tool allows patients to see if they fall within normal risk levels for their age, ethnicity, familial history of breast cancer, BRCA1 & 2 mutation positive status, and other risk factors, or do they have a higher than normal risk prediction that would encourage more frequent and/or earlier screenings coupled with greater patient compliance with completing routine screening mammograms [18]. There are three sections to this questionnaire: patient eligibility, demographics, and patient and family history (see **Figure 3**).

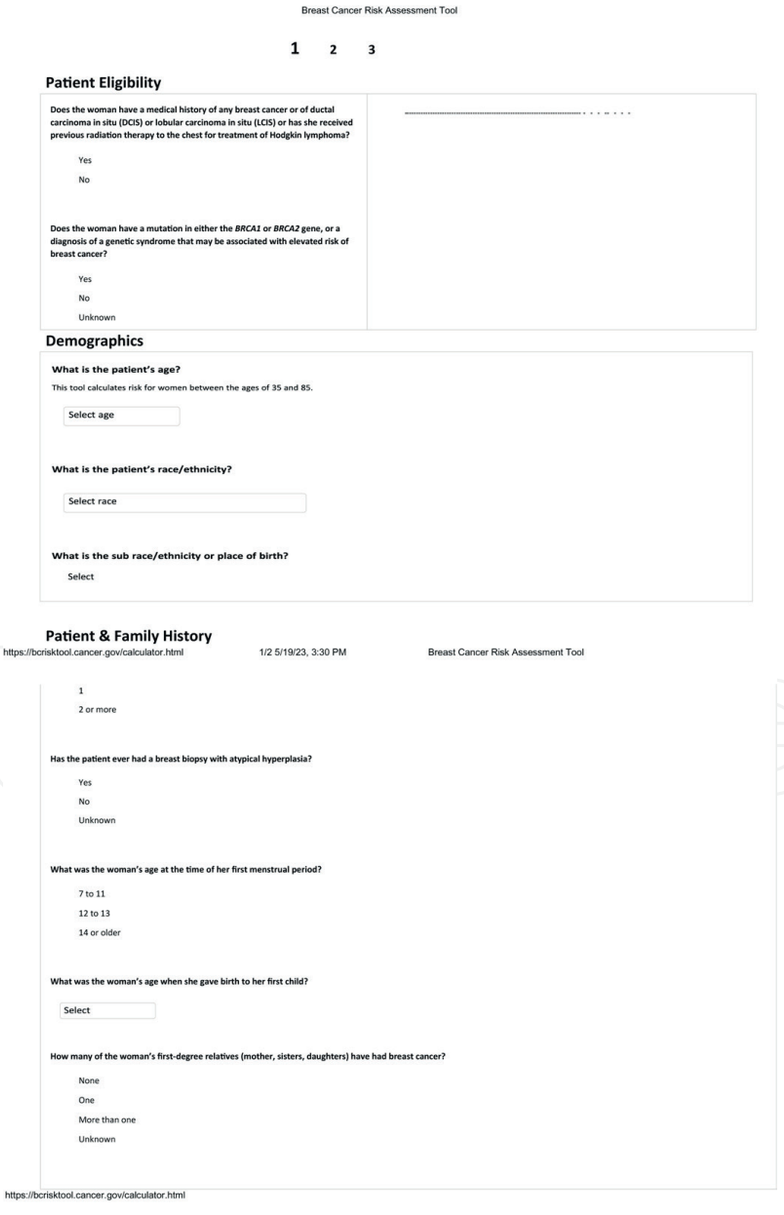

Figure 3.
Breast cancer risk assessment tool [19].

3.2 Genetic counseling and testing

There are two types of genetic mutations that differentiate the origin of the specific type of breast cancer. This will be key in genetic counseling conversations. Germline mutations are inherited because of mutations coded in either the egg and/or sperm cells, such as BRCA1 & 2 mutations that inhibits DNA repairs from occurring naturally. Then there is the somatic mutation which is not inherited and is the direct result of damaged cells with DNA repairs misaligned during restructuring. There is a proportional relationship between somatic mutations and replication accelerated in malignant cancer cells [20]. Also, since BRCA1 & 2 mutations are inherited, patients may find out about their personal risk from other family members and/or simply learn of the higher risk score because of the BCRAT questionnaire and knowledge of known family members having had breast cancer [20]. This crucial information can play an important role in a provider referring the patient to a genetic counselor and having the ability to test for this mutation and take proactive steps in routine screenings instead of waiting and worrying to see if they get breast cancer [21].

Patients with a family history of breast cancer and/or a family member with a positive BRCA1 or 2 gene mutation test will have many questions about their risk and may have scored very high on the BCRAT [19]. The ability to use a risk assessment tool to assist in support and interdisciplinary collaboration between practitioners for patient guidance sets the tone for a patient centered plan of care. Careful planning ensures what the next steps should be: genetic counseling and/or genetic testing, running additional diagnostic testing, and/or scheduling more frequent screenings [22]. Genetic testing is a personal choice and only those with this type of risk should consider having genetic testing as it is very costly and usually not covered by insurance companies. If your patient has a 20% or greater lifetime risk of getting breast cancer, positive for BRCA1 or 2 gene mutation, or has had exposure to chest radiation between the ages of 10 and 30, then they should seriously consider following the American Cancer Society's high risk for breast cancer recommendations: begin screening mammograms and Breast MRIs annually beginning at age 30 [23].

Genetic testing can be costly and have legal and ethical implications. Many people do not want others to know that they are at greater risk of breast cancer than others, especially employers. Many fear that they may not get the new job they applied for or keep their existing job, and/or be denied health insurance coverage. The Genetic Information Non-discrimination Act (GINA) of 2008 was passed for these very reasons. It protects people's privacy of genetic information and the diagnosis of a disease process from discrimination for patients in the United States. This law prevents insurance carriers from denying coverage and employers from requesting genetic information as part of the application requirement [24]. Patient confidentiality and consent for genetic testing remains a key concern for patients worried about access to their medical records. As such, part of GINA's role is to make a patient's genetic information fall under a special classification known as "health information" so that it would fall under the Health Insurance Portability and Accountability Act (HIPAA) of 2013 which frames the privacy requirements for genetic information and who has access [24].

For those that want to get evaluated for the BRCA1 & 2 gene, there are more reasonable options for testing compared to 10 years ago. Today, there are multiple private genetic testing companies that will send you a genetic test kit, that includes BRCA1 & 2 genetic testing, without a clinician's order for between $199 and up [25]. This allows women to self-refer if they do not want to go to genetic counseling before getting tested. With this ease of access to the public, clinicians need to be familiar with these

tests, their interpretation, and devising an individualized plan of care based on the report findings since patients will turn to their healthcare provider for answers if the results are confusing [20].

Patient protections have been established through the creation of molecular tumor boards (MTB). These boards are designed to ensure patients receive appropriate cancer testing and treatments derived on the premise of evidence-based plans of care based on the type of cancer, and the most applicable and effective cancer treatments. The MTB assigns a physician-oncologist that is assigned to the patient's care and responsible for their testing, treatments, and outcomes. These treatments also include targeted gene therapy considerations based on the specific genetic mutation and molecular fusion [20, 26].

4. Common signs and symptoms for concern

There are many different signs and symptoms for breast cancer that range from a lump in the breast without pain to a lump in the breast with pain, peau d'orange skin, nipple discharge, dimpling or puckering of the breast tissue, and/or obvious changes in breast or nipple appearance (inversion), pain in the axillary region, asymmetry, or swollen lymph nodes of the upper arm leading into the tail of spence [27].

4.1 Lumps

Lumps in the breast that are nodular are more easily felt before a woman's menses and usually involves tenderness. Many women have breast fibroids that are easily palpable as well and are triggered by multiple factors: caffeine use, stress, intake of certain foods such as chocolate. When performing a clinical breast exam, be sure to document the location, size, shape, thickness, consistency (solid or fluid filled), whether the lump is fixed or moveable, tenderness, any recent changes and/or trauma to the breast as well. When assessing the tenderness of the breast, the type of pain should be determined. Is the pain focal, diffuse, or cyclic in nature [9].

4.2 Nipple discharge

Nipple discharge should be evaluated for its origin: physiologic or pathologic. Is the discharge a response to normal hormonal processes in the body such as pregnancy, stress, breast feeding, changes in sleeping habits, medication induced (birth control), and/or breast stimulation? If it is related to one of these situations then it is considered to be physiologic [1, 9]. Galactorrhea is milk production in the absence of pregnancy and may be caused by certain medications such as birth control, diuretics, corticosteroids, or digitalis [1]. If the nipple discharge is only on one side, has an abrupt presence of discharge, is related to a lump/mass on the side with a discharge, and/or is serous or bloody, then there is cause for concern. This type of nipple discharge is considered pathological in origin and warrants further workups to determine the cause [9].

4.3 Diagnostic screening

Diagnostic screening for lumps in the breast has a hierarchy of sorts that can be simplified in **Table 2**.

Diagnostic Screening	Age: 30 and over w/ BRCA1 or 2 mutation	Age: less than 40 w/ lump/ mass	Age: over 40 w/ lump/ mass	Age 40 and over w/ breast augmentation
Ultrasound		X		
Mammogram	X		X	X
Breast MRI	X			

Table 2.
Diagnostic scan recommendations by age and risk [23].

Women under 40 years of age with a lump/mass identified in their breast(s) requires a diagnostic ultrasound due to the denseness of the breast; however, women over 40 have less denseness and a diagnostic mammogram is warranted. When documenting where the lumps are found, use the face of a clock to identify the location of the lump and be sure to document the shape, size, consistency, and moveability of the lump of each corresponding lump when ordering the diagnostic mammogram or ultrasound. This information is helpful to the radiology facility [1].

Those with a known BRCA1 or 2 mutation should begin MRI and diagnostic mammogram screenings annually at age 30 to ensure early detection [23]. Maintaining a consistency with a specific radiology facility is important. Having one site where one's ultrasound, mammogram, and/or MRIs are completed provides a history of past scans which allows for comparison between the current ultrasound, MRI, or mammogram and past ultrasound, MRI, or mammograms to determine if there is a change in the breasts as well as the severity of the change from one year to the next (**Figure 4**) [20].

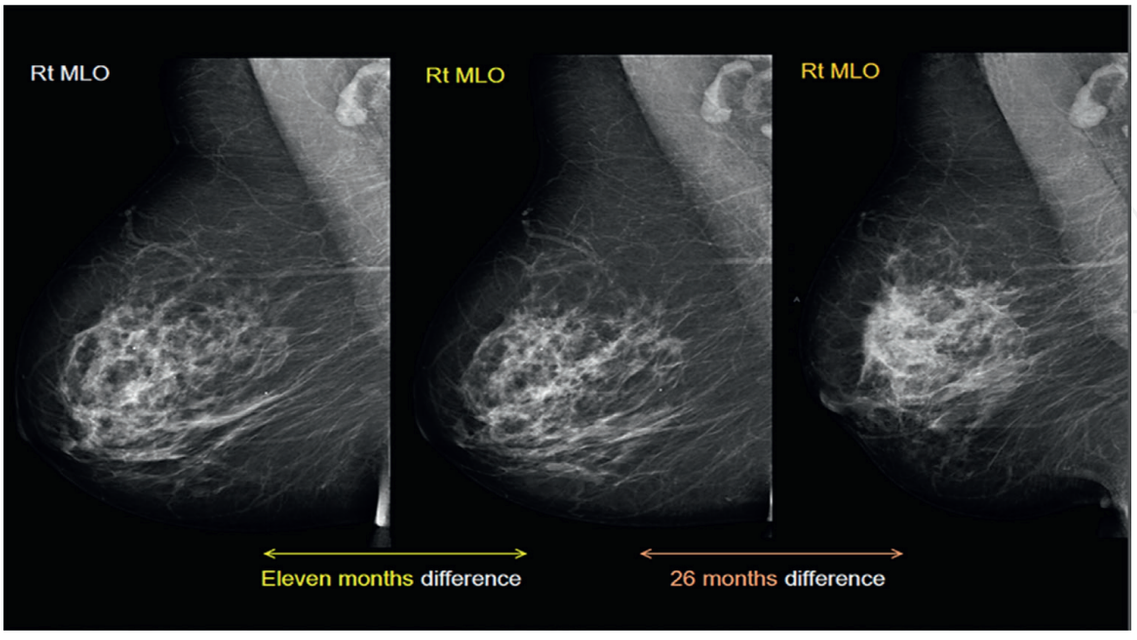

Figure 4.
Bilateral breast cancer radiologic pathologic correlation [28]. Permission granted to share this image compliments of Dr. László Tabár.

5. Breast cancer

Cancer is a mutation of healthy cells whose DNA was not repaired back to a homogenous status. This mutation is expressed through biomarkers and molecular subtypes that drive the severity and prognosis of said cancers [29]. The BRCA gene has gotten skewed in its role in breast cancer. Its primary role is to repair damaged DNA and is considered to be a tumor suppressor, but with a mutated form of this gene, it can cause breast cancer and this is what this gene is now known for, not its original function [30]. The BRCA1 & 2 gene mutation is one culprit of a familial genetic mutation identified through whole gene sequencing [31]. Patients can be evaluated for the BRCA1 & 2 mutation and know whether they carry this mutated form of the gene and take precautions to proactively screen more frequently and/or make informed decisions about their plan of care, options, and further testing for tumor markers. The individualized plan of care and having the knowledge that the risk is greater for breast cancer may assist in a more active role between the patient and their provider to ensure early detection remains the focus [29]. Why is this so important? Women with this mutation have a much higher risk of developing breast cancer compared to the general population without this genetic mutation (see **Table 3**). The Online Mendelain Inheritance in Man (OMIM) provides guidance on the BRCA1 & 2 gene phenotype relationship in relation to the chromosomal location, inheritance, mapping, and gene/locus (see **Table 4**). Also, women with a history of epithelial ovarian cancer should consider being tested for the BRCA gene mutation and any other cancer genes that align with ovarian cancer risk [30].

Over 80% of BRCA1 mutations lose its ability to differentiate breast stem cells and as a result it cannot express three specific receptors: human epidermal growth factor, estrogen, and progesterone. BRCA2 mutations have a higher rate of ovarian cancer compared to BRCA1 mutations. Studies have found that to reduce the risk of breast and/or ovarian cancer for those with either BRCA1 or 2 mutation is to proactively have an oophorectomy [33]. This could be due to the decline in hormone fluctuation, especially hormone receptor sensitive breast cancers.

5.1 Diagnostic testing, prognosis, and susceptibility

There are advanced diagnostic testing options rooted in next-generation sequencing technology that is available when testing for specific breast cancer mutations. Clinicians can order these tests once a diagnosis of breast cancer is determined. These include the following: next-generation sequencing (NGS), sequenced analytic data pipelines derived from NGS, anchored multiplex polymerase chain reaction (AMP) also derived from NGS. Other tests that determine the aggressive nature of the cancer, its recurrence risk, and what adjuvant therapies are needed based on genetic analysis:

Breast cancer	Percentage who gets breast cancer over a lifetime up to between age 70–80
BRCA1 mutation positive	55–72%
BRCA2 mutation positive	45–69%
General population without BRCA gene mutation	13%

Table 3.
Percentage of breast cancer patient comparisons [30].

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Gene / locus	Gene/locus MIM #	Phenotype: familial, breast-ovarian cancer	Phenotype map	Phenotype MIM #	Inheritance: autosomal dominant	Inheritance: multifactorial	Chromosomal location
BRCA1	113,705	Yes	3	604,370	Yes	Yes	17q21.31
BRCA2	600,185	Yes	3	612,555	Yes	No	13q13.1
RAD51C	602,774	Yes, susceptibility to, 3	3	613,399			17q22
RAD51D	602,954	Yes, susceptibility to, 4	3	614,291			17q12
TP53		Breast cancer	1				17p13.3

MIM = Mendelian Inheritance in Man. Phenotype map legend: 1 = underlying defect unknown, but mapped; 2 = mapped with statistical methods; 3 = disorder's molecular basis is known; and 4 = multiple gene involvement.

Table 4.
Breast cancer phenotype-gene correlation [32–36].

Test detections	BRCA1 & 2	Next-generation sequencing	Sequenced analytic data pipelines	Anchored multiplex polymerase chain reaction
BRCA gene mutation	X	X	X	X
DNA variant		X	X	X
DNA fusion		X	X	X
Adjuvant therapy susceptibility		X	X	X

Table 5.
Breast cancer testing considerations [20, 37].

(1) MammaPrint uses 70 genes to test for prognosis and the adjuvant therapy susceptibility and (2) Oncotype DX Breast Recurrence Score Test uses a 21 gene scoring system to determine cancer recurrence, cancer aggression, and susceptibility to adjuvant therapy [20]. All of these tests provide a different function/use in testing that varies from identifying if cancer is present at all to specific breast cancer variants, instability, fusion of DNA, and/or identifying specific markers that make the cancer cells more susceptible and responsive to adjuvant treatment modalities [20]. The most advanced tests identify the rearrangement of chromosomal intergenic fusion (see **Table 5**). Both types of genetic mutations, germline and somatic can be individually fused or a mix of both and can be found in later stages of metastatic cancers [20]. Specific fusions are associated with molecular subtype ER+ metastatic cancers in the later cancer stages [20]. One promising test that can be done with NGS is to profile the cancer and its susceptibility of adjuvant therapy for cell-free DNA (cfDNA) found in plasma [37]. Circulating tumor DNA (ctDNA) are also found in plasma and helps to determine the risk of recurrence of cancer after remission [38].

The type of biomarkers and molecular subtypes play a significant role in the tumor growth and prognosis of this type of breast cancer (see **Table 6**).

Early detection/diagnosis of breast cancer is crucial in determining treatment plans and improving the chance for a positive response to treatments to achieve remission. Those that are diagnosed with a localized early-stage breast cancer (in situ) is 66% [10]. The five-year survival rate for the different stages when diagnosed is as follows: localized breast cancer = 99%, regional breast cancer = 86%, and distant breast cancer = 30% [10]. Invasive breast cancer is cancer that has spread through the blood or lymph nodes to other parts of the body, also known as metastasis. The percentage of breast cancers that are invasive is 83% [10]. This number is alarming and the advancements in targeted gene and immunotherapy are new tools in fighting breast cancer and improving survival rates [10, 20].

5.2 Treatment options

Traditional cancer treatments are chemotherapy, radiation therapy, hormone blocking therapy, and surgery (lumpectomy or mastectomy). Patients with a mastectomy may consider breast reconstruction surgery and should discuss this with their surgeon about when would be the best time to undergo this type of procedure based on their treatment plan [10]. Chemotherapy and hormone therapy has been around for a long time; however, the next promising therapies to impact treatment

	Estrogen Receptor (ER) + (HR+)		Hormone Receptor Negative (HR−)	HR-
Molecular subtype	**HER2- (Luminal A)**	**HER2+ (Luminal B) Ki61**	**HER2+ (ER−, HER2−, PR−) triple negative breast cancer (TNBC) basal-subtype**	**HER2+ (enriched)**
% of all breast cancers	68%	10%	10%	4%
Growth of tumor	Slow	Fast	Aggressive	Aggressive
Prognosis	Good	Poor	Poor	Improved w/ targeted gene therapy
Cancer cell grade	Lower	Higher	Higher	Higher
5-year survival rate	94%	91%	85%	77%

Table 6.
Breast cancer biomarkers and molecular subtypes [10].

modalities include non-viral targeted gene therapy and immunotherapy. These cutting edge therapies joined the fight against breast cancer as adjuvant therapy, usually in combination with traditional therapies [10]. In pursuit of treating patients with the most effective treatment allowed, one such newcomer over the last few years has been precision therapy where oncogene drivers are used in individualized treatments using the molecular makeup of the patient to combat cancer cells with targeted gene therapy [20]. The impact of molecular subtypes on treatment and patient outcomes is reflected in **Table 7**. Immunotherapy is an innovative approach in fighting breast cancer by using one's own immune system to target and kill cancer cells. This type of therapy is called checkpoint inhibitors and is being used for TNBC.

The molecular subtype represents the hormone receptor status for estrogen, progesterone, and human epidermal growth receptor 2 (HER2). Based on the hormone receptor affinity, you can see the correlation for subtype, the Ki-67 recurrence predictor for cell division/replication, prognosis, therapy type, and treatment options. TNBC has the poorest prognosis, but recent clinical trials have proved positive in slowing the progression of metastatic or recurring TNBC, although some side effects are worse than traditional therapies. Sacituzumab Govitecan (Trodelvy) is a drug approved by the FDA in 2021 and is showing great promise for TNBC patients [41].

There are other new innovative research studies that have found that breast cancer stem cells (CSC) can achieve apoptosis with the use of specific PDE4 inhibitors (anti-inflammatory medications) [42]. One study found that there is a signaling pathway to turn on cancer stem cells to survive through upregulation of PI3K/AKT/mTOR which increase CSC levels and in turn increases PDE4 levels. If these pathways can be turned on then they can be turned off. In turning off the pathway, it can stop the cyclic adenosine monophosphate (cAMP) from binding to regulatory subunits of inactive protein kinase A (PKA); thereby, stopping the conversion to an active form of (PKA) to trigger AKT and mTOR. Turning off this pathway will turn on autophagy of CSC and lead to cell death of the cancer cell. This cascade of signaling pathways is crucial

Molecular subtype	HER2− Luminal A	HER2+/ PR+/− Luminal B	TNBC	HER2+Enriched
HR+/−	Estrogen+/ PR+	Estrogen+/ PR+	HR−/PR−/HER2−	HR−/PR−
Ki-67 proliferative index/recurrence predictor	</equal 14%	>/equal 14%	Any	Any
Prognosis	Good/slow	Poor/fast	Poor/highly aggressive w/ metastasis	Poor/highly aggressive
Therapy type	Estrogen deprivation	Estrogen deprivation	Precision therapy	Precision therapy
Oncogenic fusion therapy resistance	Increased risk	Increased risk	Need further susceptible pathways for effective treatment	Need further susceptible pathways for effective treatment
Treatment plan to fusion/ mutation	Combination therapy	Combination therapy	Combination therapy	Combination therapy

Table 7.
Molecular subtypes on treatment and outcomes [20, 39, 40].

in stopping phosphatidylinositol-3-kinase (PI3K) from proliferating CSC growth. CSCs were found to have elevated PDE4 levels when compared to healthy stem cells. Thus, the use of PDE4 inhibitors may hold the key to the downregulation of PI3K/AKT pathway, thus reducing resistance to chemotherapy in CSCs [42]. This study found that PKA and cAMP levels antagonized the signaling pathway "PI3K/AKT/mTOR" and caused "cell cycle arrest" [42].

5.3 Breast cancer incidence, mortality rate, and the disparity gap

The disparity gap for breast cancer incidence is not what one might expect with Caucasians having the highest breast cancer incidence rate followed by Black women per every 100,000 women in the United States (see **Table 8**). The mortality rate is similarly surprising with Asian women having the lowest mortality rate and Hispanic women having the second lowest mortality rate compared to Caucasian women with the third lowest mortality rate, whereas Black women had the highest mortality rate. Accordingly, between 2012 and 2018, there was a 9% disparity gap between Black women compared to Caucasian and Asian Pacific Island women for a 5-year relative

Breast cancer rate per 100,000	Caucasian	Black	Native American	Asian	Hispanic
Incidence	133.7	127.8	111.3	101.3	99.2
Mortality	19.7	27.6	20.5	11.7	13.7

Table 8.
Breast cancer incidence and mortality rates by ethnicity in the US from 2016 to 2020 [10].

survival rate, 83% vs. 92%. This difference in survival rate translates into more deaths in black women across the spectrum due to differences in access to care and insurance coverage/financial ability to pay for treatments [10]. The disparity gap for breast cancer survivors with late-stage breast cancer (stage 4) has begun to decrease steadily. This disparity gap has been zeroed out among racial/ethnic groups as a result of the Medicaid expansion programs implemented over the last couple of years [10]. Survival rates that are consistent with the elimination of disparity gaps will continue to take time, but as noted in late-stage breast cancers, this too is achievable.

Five percent of breast cancer survivors will face the daunting diagnosis of cancer once more after remission. When looking at the recurrence of breast cancer in women, there is a 70% chance that it will be in the opposite breast (contralateral). One study's findings reported that black women had a 44% greater chance of this recurrence whereas Hispanic women had an 11% greater chance of the same recurrence in the opposite breast compared to their Caucasian counterparts [10].

6. Conclusion

The breast, in many ways, defines a young girl's journey into womanhood, motherhood, and old age, ever changing along the way [1]. With older age being one of the main risk factors for breast cancer and the changes that come with aging, it provides insight into the body's own shortcomings physically and genetically. Breast cancer impacts patients in many ways: physically, financially, emotionally, and functionally; however, advanced technologies in genomics through mapping of the human genome, next-generation sequencing, and evidence-based treatments all combined is helping to unlock the mystery of many disease processes, including breast cancer. This innovative science is changing the course of how we see, treat, and think about patient care, outcomes, and what is possible. The more we learn, the more impact we can have on patient care, treatment plans, and improved patient outcomes. We are on the cusp of a new scientific era, but new advancements in breast cancer treatments are still needed to continually strive to cure cancer for today's cancer patients and future generations to come [20].

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Jarvis C. Physical Examination and Health Assessment. 7th ed. St. Louis, Missouri: W. B. Saunders; 2016

[2] Dains, J.E., L.C. Baumann, and P. Scheibel, Advanced Health Assessment and Clinical Diagnosis in Primary Care. 6th ed. 2020, St. Louis, Missouri, Elsevier.

[3] Lynch PM. Breast Anatomy Normal Scheme, B.A.N. Scheme, Editor. 2006. Cc BY 3.0

[4] Memorial Sloan Kettering Cancer Center. Anatomy of the Breast. 2023. Available from: https://www.mskcc.org/cancer-care/types/breast/anatomy-breast

[5] Pillay J, Davis TJ. Physiology, lactation. In: StatPearls. StatPearls Publishing LLC: Treasure Island (FL); 2023

[6] Cancer Research UK; Wikipedia Commons, Lymph Nodes in and Around the Breast, L.N.i.a.A.t. Breast, Editor. 2016

[7] Society, AC Lymph Nodes and Cancer. 2023. Available from: https://www.cancer.org/cancer/diagnosis-staging/lymph-nodes-and-cancer.html

[8] Sattari M, Serwint JR, Levine DM. Maternal implications of breastfeeding: A review for the internist. The American Journal of Medicine. 2019;**132**(8):912-920

[9] Bickley L. Bates' Guide to Physical Examination and History Taking. 13th ed. Philadelphia, PA: Wolters Kluwer; 2021

[10] American Cancer Society. Breast Cancer Facts and Figures: 2022-2024. GA: Atlanta; 2022

[11] Li CM et al. Aging-associated alterations in mammary epithelia and stroma revealed by single-cell RNA sequencing. Cell Reports. 2020;**33**(13):108566

[12] Mantovani A. The inflammation—Cancer connection. The FEBS Journal. 2018;**285**(4):638-640

[13] Huelse JM et al. MERTK in cancer therapy: Targeting the receptor tyrosine kinase in tumor cells and the immune system. Pharmacology & Therapeutics. 2020;**213**:107577

[14] U.S. Preventive Services Task Force. Final Update Summary: BRCA Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing. 2016. Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing

[15] National Breast Cancer Foundation. Breast Self-Exam. 2023. Available from: https://www.nationalbreastcancer.org/breast-self-exam/

[16] U. S. Preventive Services Task Force. Breast cancer screening. 2016. Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/breast-cancer-screening

[17] Banegas MP et al. Evaluating breast cancer risk projections for Hispanic women. Breast Cancer Research and Treatment. 2012;**132**(1):1-11

[18] Walker-Smith TL, Baldwin S. A quality improvement initiative: Improving mammogram screening rates among low-income Hispanic women

in primary care. Journal of Doctoral Nursing Practice. 2020;**13**(1):71-78

[19] National Cancer Institute. Breast Cancer Risk Assessment Tool: Risk Calculator. 2023. Available from: https://bcrisktool.cancer.gov/calculator.html

[20] Walker-Smith TL, Peck J. Genetic and genomic advances in breast cancer diagnosis and treatment. Nursing for Women's Health. 2019;**23**(6):518-525

[21] Haas JS et al. Provider attitudes and screening practices following changes in breast and cervical cancer screening guidelines. Journal of General Internal Medicine. 2016;**31**(1):52-59

[22] Gabram SGA et al. Assessing breast cancer risk and providing treatment recommendations: Immediate impact of an educational session. Breast Journal. 2009;**15**:39-45

[23] Susan G. Komen. Breast Cancer Screening for Women at Higher Risk. 2022. Available from: https://www.komen.org/breast-cancer/screening/when-to-screen/high-risk-women/

[24] National Human Genome Research Institute. Genetic Discrimination. 2022. Available from: https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination

[25] 23andme. Health+Ancestry Service. 2023. Available from: https://www.23andme.com/dna-health-ancestry/

[26] Merry D et al. Trust and responsibility in molecular tumour boards. Bioethics. 2018;**32**(7):464-472

[27] American Cancer Society. Breast Cancer Signs and symptoms. 2023. Available from: https://www.cancer.org/cancer/types/breast-cancer/screening-tests-and-early-detection/breast-cancer-signs-and-symptoms.html

[28] Global Radiology CME. Bilateral Breast Cancer Radiologic Pathologic Correlation. 2017. Available from: https://static.wixstatic.com/media/e35976_5474bc88964c430cb8cdb27282344b1d~mv2.png/v1/fill/w_1000,h_743,al_c,usm_0.66_1.00_0.01/e35976_5474bc88964c430cb8cdb27282344b1d~mv2.png

[29] Walker-Smith T, Murphey C, Peck JL, CME. Addressing whole-genome sequencing and breast cancer in primary care. Clinical Advisor. 2019;**22**(1):24-31

[30] Institute, N.C. BRCA Gene Mutations: Cancer Risk and Genetic Testing. 2020. Available from: https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet

[31] Sokolenko AP et al. Identification of novel hereditary cancer genes by whole exome sequencing. Cancer Letters. 2015;**369**(2):274-288

[32] Online Mendelian Inheritance in Man Breast-ovarian Cancer, Familial, Susceptibility to, 1; BROVCA1. 2016. Available from: http://omim.org/entry/604370?search=BRCA1&highlight=brca1

[33] Online Mendelian Inheritance in Man. Breast-ovarian Cancer, Familial, Susceptibility to, 2; BROVCA2. 2016. Available from: http://omim.org/entry/612555?search=BRCA2&highlight=brca2

[34] OMIM. Breast-Ovarian Cancer, Familial, Susceptibility to, 3; BROVCA3. 2021. Available from: https://www.omim.org/entry/613399?search=Breast%20cancer&highlight=breast%20cancer%20cancerous

[35] OMIM. Breast-Ovarian Cancer, Familial, Susceptibility to, 4; BROVCA4.

2011. Available from: https://www.omim.org/entry/614291

[36] OMIM. Breast Cancer-Related Regulator of TP53. 2017. Available from: https://www.omim.org/entry/113721?search=Breast%20cancer&highlight=breast%20cancer%20cancerous

[37] Esposito, Abate R et al. Next generation sequencing-based profiling of cell free DNA in patients with advanced non-small cell lung cancer: Advantages and pitfalls. Cancers (Basel). 2020;**12**(12):2-3

[38] Niravath P, Cakar B, Ellis M. The role of genetic testing in the selection of therapy for breast cancer. JAMA Oncology. 2017;**3**(2):262-268

[39] Chiu AM et al. Integrative analysis of the inter-tumoral heterogeneity of triple-negative breast cancer. Scientific Reports. 2018;**8**:11807

[40] Mohammed AA. The clinical behavior of different molecular subtypes of breast cancer. Cancer Treatment and Research Communications. 2021;**29**:100469

[41] Loibl S et al. Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer. European Journal of Cancer. 2023;**178**:23-33

[42] Mukherjee P et al. PDE4 inhibitor eliminates breast cancer stem cells via noncanonical activation of mTOR. Journal of Cellular Biochemistry. 2022;**123**(12):1980-1996