Last Section Update: 10/2025

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1 Understanding Breast Cancer

Breast cancer is one of the most common cancers among women in the United States, second only to skin cancer.[1] It accounts for one in three new cancers in women each year and is the second most common cause of cancer-related death in American women (the most common being lung cancer).[2] Men can also get breast cancer and account for about 1% of cases.[3] The American Cancer Society estimated that, in women in the United States, about 317,000 invasive breast cancer diagnoses and about 42,000 breast cancer-related deaths would occur in 2025.[4]

Fortunately, breast cancer treatment has made significant progress over the past several decades. Advances in screening and earlier diagnosis,[5] targeted therapies and personalized medicine, as well as improved surgical techniques and greater knowledge about the importance of a healthy diet and lifestyle, mean that women now have a greater likelihood of positive outcomes than in decades past. For instance, the breast cancer death rate has fallen by 44% since 1989. Currently, about 86% of women live for at least 10 years after a breast cancer diagnosis in the United States.[6]

In this Life Extension Breast Cancer Treatment Protocol, you will learn about current and emerging treatment options, including the latest advances in precision medicine and how treatments can be tailored to your unique characteristics and preferences. You will also find a summary of the evidence on several dietary and lifestyle changes, as well as targeted nutritional interventions, that may have a role in the context of breast cancer treatment. Note that this overview does not cover breast cancer prevention. We at Life Extension encourage you to read and share this information with your healthcare team.

Other Life Extension Protocols that may be relevant for those receiving treatment for breast cancer include:

- **Chemotherapy**
- **Cancer Radiation Therapy**
- **Cancer Surgery**

What Is Breast Cancer?

Breast cancer starts when some breast cells begin to grow out of control and form abnormal growths or lumps. Not all breast lumps are malignant (cancerous), but all lumps should be evaluated by a healthcare professional.[1]

Types of Breast Cancer

The breast is composed of different types of cells that form ducts, glands, and fatty tissue. The tissue type in which a cancer arises, in addition to individual characteristics of the patient and tumor, determine how breast cancers are classified and how treatment choices are made.[1,3]

Ductal cancers, which arise from the ductal structures of the breast that carry milk to the nipple, are the most common type of breast cancer, making up about 75% of all cases.[1,7] Lobular cancers start in the glandular cells where breast milk is produced and make up about 8% of total breast cancer cases, and mixed ductal and lobular cancers account for another 5%. Cancers that arise in blood vessels or connective tissues of the breast are less common and may require a specialized treatment approach.[1,7]

Table 1. Breast Cancer Classification by Tissue of Origin

Type	*Characteristics*
Ductal Breast Cancers	
Ductal carcinoma in situ (DCIS)[8,9]	Non-invasive or pre-invasive Does not extend beyond the duct wall
Invasive ductal carcinoma (IDC)[1]	Most common type of breast cancer Ductal cancer that has spread beyond the duct wall into the surrounding breast tissue
Lobular Breast Cancer	
Lobular carcinoma in situ (LCIS)[3,10]	Benign; not classified as breast cancer
Invasive lobular carcinoma (ILC)[1]	Has spread to the surrounding breast tissue Less common than IDC More likely to affect both breasts than other invasive breast cancers
Inflammatory Breast Cancer	
Inflammatory breast cancer (IBC)[1]	Rare and aggressive type of invasive breast cancer Causes edema (swelling) and redness of the skin of the breast, giving the appearance of breast inflammation

Ductal breast cancers

Ductal breast cancer, the most common type of breast cancer, arises in the ductal structures of the breast, usually from the epithelial cells that line the ducts.[1]

Ductal carcinoma in situ (DCIS) is a type of non-invasive or pre-invasive breast cancer that does not extend beyond the duct wall. DCIS tumors are usually found with a screening mammogram, though ultrasound, magnetic resonance imaging (MRI), and biopsy can also play a role in diagnosis.[8,9] The diagnosis of DCIS has increased

more than 10-fold since the widespread adoption of mammography screening. Approximately 20% of new breast cancer diagnoses are DCIS.[1,8] Nearly all women with DCIS can be cured, but, if left untreated, about 40% of cases progress to invasive breast cancer.[1,11]

Invasive ductal carcinoma (IDC) is the most common type of breast cancer, making up approximately 70–80% of cases, and is characterized as ductal cancer that has spread beyond the duct wall into the surrounding breast tissue.[1]

Lobular breast cancer

Lobular breast cancer arises in a milk-producing gland, or lobule.[1]

Lobular carcinoma in situ (LCIS) is now considered a benign entity and is no longer classified as breast cancer in the most recent American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[3,10]

Invasive lobular carcinoma (ILC) has spread to the surrounding breast tissue. It is less common than IDC, making up approximately 10% of total breast cancer cases, and is more likely to affect both breasts than other invasive breast cancers.[1]

Inflammatory breast cancer

Inflammatory breast cancer (IBC) is a rare and aggressive type of invasive breast cancer in which cancer cells block lymph vessels in the skin of the breast.[1] This causes edema (swelling) and redness of the skin of the breast, giving the appearance of breast inflammation. About 1–5% of all breast cancers are IBC.[1]

Inflammatory breast cancer may not cause a discreet lump or mass and is sometimes not detectable on a mammogram. It is always invasive, at least locally, at the time of diagnosis since it has already spread into the skin. Compared with other types of breast cancer, IBC is more common in younger women, grows and spreads more rapidly, and has a worse prognosis.[1]

Classification by receptor subtypes

Receptors on the surfaces of breast cancer cells have become an important means of classifying tumors into subtypes to provide more personalized treatment strategies. Testing for the presence of these markers is done in all patients with invasive breast cancer who undergo biopsy or surgery.[12]

Table 2. Breast Cancer Classification by Receptor Subtype

Receptor Status	Characteristics
Hormone receptor (HR)-positive or HR-negative[12,13]	Breast cancers that express estrogen receptors (ERs) and/or progesterone receptors (PRs) in at least 1% of tested cells are HR-positive, while those that do not are HR-negative
Human epidermal growth factor receptor 2 (HER2)-positive or HER2-negative[12,14]	Express high levels of HER2 (sometimes called ERBB2) or have an abnormally high number of the *HER2* gene copies
HER2-low[15,16]	HER2 expression just below the threshold for HER2-positivity and without an excess of the *HER2* gene
Triple-negative[1]	Breast cancers that have neither ERs, PRs, nor high levels of HER2 are called triple-negative breast cancer (TNBC)

The breast cancer receptor subtypes are:

- **Hormone receptor (HR)-positive or HR-negative.** Breast cancers that express estrogen receptors (ERs) and/or progesterone receptors (PRs) in at least 1% of tested cells are HR-positive, while those that do not are HR-negative. They may be further classified as ER-positive or ER-negative and PR-positive or PR-negative. About 75% of women with breast cancer have tumors that are ER-positive, and more than 50% of these are

also PR-positive, while very few cases are solely PR-positive.[12,13] Hormone receptor status determines which treatments will be effective. ER-positive breast cancers are likely to respond to endocrine therapies that lower estrogen levels or block ERs.[12,14] PR-positivity is associated with lower risk of recurrence and longer survival, while PR-negativity is usually an indicator of more aggressive cancer with poorer outcomes.[13]

- **Human epidermal growth factor receptor 2 (HER2)-positive or HER2-negative.** Breast cancers that express high levels of HER2 (sometimes called ERBB2) or have an abnormally high number of the *HER2* gene copies are HER2-positive, while those that do not are HER2-negative. About 15–20% of breast cancers are HER2-positive. They are typically fast-growing but are likely to respond to HER2-targeted therapies, such as the monoclonal antibody trastuzumab (Herceptin).[12] If the level of receptor expression is uncertain, a test that counts copies of the *HER2* gene in cancer cells can be done. Tumors that have too many copies of *HER2* are also classified as HER2-positive.[12,14]
- **HER2-low.** A new category of HER2 expression has recently emerged: HER2-low. Tumors with HER2 expression just below the threshold for HER2-positivity and without an excess of the *HER2* gene can now be classified as HER2-low and may be susceptible to certain HER2-targeting therapies.[15] Recent estimates suggest 45–55% of breast cancers are HER2-low, and most of these are HR-positive.[16]
- **Triple-negative**. Breast cancers that have neither ERs, PRs, nor high levels of HER2 are called triple-negative breast cancer (TNBC). Triple-negative breast cancer grows and spreads faster than other types of breast cancer. It does not respond to receptor-targeting therapies so is typically treated with chemotherapy, alone or in combination with immunotherapy. In general, TNBC is difficult to treat and has a worse prognosis than receptor-positive breast cancers. About 15% of breast cancers are TNBC.[1]

2 Diagnosis and Staging

Symptoms and Early Detection

Early-stage breast cancer can sometimes cause symptoms, but many cases are identified through screening in people who do not have symptoms.[17]

Signs and symptoms

The most common finding related to breast cancer is a new irregularly shaped lump or change that can be felt in the breast. These lumps are often painless and hard but can also be soft, painful, tender, or more rounded, and all new breast lumps should be evaluated by a healthcare professional. Other symptoms may include swelling, skin dimpling (feels like the skin of an orange), skin reddening, changes in the size or shape of the breast, pain in the breast or nipple, other nipple changes (eg, nipple turning inward, flaking and/or red skin, discharge), and swollen lymph nodes under the arm or above the collar bone.[14,17]

Breast self-examination

There is little evidence that regular breast self-examination decreases breast cancer mortality, but it is generally recommended that women be familiar with the way their breasts look and feel in order to detect any changes that might arise.[8,17] Many women like to keep track of their breast health by doing breast self-exams on a regular basis; for example, while showering or dressing. However, there is no firm recommendation on when and how to do this.[17]

Screening methods

Breast cancer is often easier to treat successfully when it is detected at an early stage, before the tumor has grown and spread. Regular screening can help identify breast cancer early.[17]

Screening recommendations vary depending on age and the number of risk factors. Women who have a strong family history of breast cancer, a genetic mutation known to increase breast cancer risk (eg, *BRCA1* or *BRCA2*), or received chest radiation before the age of 30 are considered to be at high risk, while women without any of these are considered to be at average risk.[17]

Most breast cancer screening recommendations in the United States agree that women with average risk should have screening mammograms every one to two years from the age of 40–44 years until age 69.[18] Many recommendations also suggest healthcare providers perform annual breast exams for women under 40.[18] Generally, mammograms are suggested every one to two years after age 70 for women who have at least 10 years

of remaining life expectancy.[18] In women with high breast cancer risk, a screening mammogram and breast MRI are recommended annually starting at age 30–35, depending on family and patient history.[17,18]

Mammograms

A mammogram is a low-dose X-ray of the breast that can detect abnormalities in breast tissue.[8,17] In the United States, about 10% of women who undergo mammography are asked to return for additional tests, such as a biopsy to further evaluate an abnormality seen on the mammogram.[8] During a mammogram, the breasts are compressed, one at a time, between two plates in order to reduce the thickness of the tissue and, thus, the amount of radiation needed to get a good image of the breast.[8] Two images of each breast are generally taken.[17]

A three-dimensional (3D) mammography technique called breast tomosynthesis or digital breast tomosynthesis (DBT) is increasingly being used as an alternative to standard two-dimensional (2D) mammography screening. In DBT, a number of 2D images are taken at various angles and then reconstructed by a computer to provide a 3D image.[8,17] This technique may reduce the number of women who are called back for further evaluation and may be more helpful for women with dense breast tissue.[17] Several large studies are being conducted to test the value of this new technique compared with conventional 2D imaging.[8,17]

Ultrasound

Ultrasound is a non-invasive imaging technique that uses sound waves generated by a handheld instrument that is moved over the skin to detect differences in tissue densities. Ultrasound is not typically used for screening but can be helpful if a woman feels a change in her breast that is not detected by mammography. Ultrasound can also be used in addition to standard mammography in women with dense breast tissue. Mammography is less sensitive at detecting small masses in dense breast tissue, which is present in 43% of women age 40–74.[8,19] Follow-up ultrasound may also be recommended if a suspicious area is detected on a mammogram, since ultrasound is better at distinguishing benign changes, such as fluid-filled cysts, from potentially cancerous solid masses.[19]

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an imaging tool that uses radio waves and strong magnets to detect tissue differences.[20] Its use, in conjunction with mammography, is recommended as a screening method for women at high risk for breast cancer, since these techniques complement each other.[17,18] MRI can detect some cancers that cannot be identified by mammography but is also more likely to generate false positive findings that result in patients being subject to unnecessary testing, such as biopsy.[17]

Diagnostic Procedures

Breast cancer diagnosis involves a series of tests to confirm that a symptom or suspicious area detected in the breast during screening is breast cancer. Once the diagnosis is confirmed, additional tests are done to classify the tumor and determine whether it has spread within the breast or to other parts of the body. These are all important considerations in determining the stage of the cancer, the patient's prognosis, and the treatment approach.[14,17]

Clinical examination

Clinical examination for the possibility of breast cancer involves the healthcare provider gathering a medical history, performing a thorough physical examination, including a breast exam, and ordering imaging tests to get a complete picture of the patient's disease. In addition, a biopsy provides critical information about the tumor, and blood tests may be ordered to assess a patient's general health.[14]

Imaging techniques

The imaging techniques used in diagnosis of breast cancer are the same as those used in screening, including mammogram, ultrasound, and MRI, and their use may vary depending on the type of breast cancer suspected and features of the area, such as size and depth within the breast.[21] Ultrasound and MRI may also be used to guide biopsy procedures.[17]

Biopsy techniques

Biopsy is an important aspect of cancer diagnosis and involves removing a small sample of the suspicious breast

area in order to analyze it in the laboratory to confirm whether or not cancer is present.[17] There are different types of biopsy, depending on where the suspected area is, its size, whether there is more than one suspicious area, and the patient's health and preferences.[17]

Most biopsies are done with a needle in the office rather than as surgical procedures. Fine needle aspiration biopsy involves the insertion of a very fine needle into the breast to remove a liquid or small tissue sample. Core needle biopsy uses a larger needle and removes a larger sample than fine needle aspiration.[17] Ultrasound or MRI may be used to guide these procedures. Sometimes, surgical biopsy is required to remove the lump or area of concern from the breast. A biopsy sample of lymph nodes under the arm may also be taken, as the spread of cancer to other parts of the body often occurs via the lymph system.[14,17]

Evaluation for metastatic disease

When a cancer spreads from the place it originally developed, such as the breast, to another part of the body, this is termed metastatic disease.[14] If metastatic disease is suspected, whole-body imaging and possibly biopsy procedures may be performed, depending on the results from the original diagnostic testing, patient symptoms, and physical exam findings.[22]

Genetic Testing

About 5–10% of breast cancers are related to inherited (germline) gene mutations. Genetic testing can be helpful for understanding how breast cancer might respond to treatment, whether targeted therapies might be appropriate, and the risk of other cancers.[23]

Variants (or mutations) of two *BRCA* genes, *BRCA1* and *BRCA2*, are important inherited contributors to breast cancer risk in women and men. Because the proteins encoded by *BRCA1* and *BRCA2* are involved in DNA repair and tumor suppression, mutations can lead to abnormal cell growth and increase the likelihood of cancer. In fact, the presence of a *BRCA* mutation raises a woman's risk of breast cancer to as high as 70% by the age of 80 years. It also increases the risk of ovarian and other cancers.[23] Other germline mutations associated with increased breast cancer risk include *ATM*, *PTEN*, *CHEK2*, *CDH1*, and *PALB2*.[23]

Genetic testing can help identify people with a familial risk of breast cancer. While some experts recommend genetic testing be offered to all patients with breast cancer, the National Comprehensive Cancer Network suggests genetic testing be reserved for patients who have or have had breast cancer and meet any of the following criteria[22]:

- Breast cancer diagnosed at age ≤50 years old
- Triple-negative breast cancer
- Multiple primary breast cancers
- Lobular breast cancer in addition to a personal or family history of gastric cancer
- Male breast cancer
- Ashkenazi Jewish ancestry
- Family history (ie, first-, second-, and third-degree relatives on the same side of the family) of breast cancer at ≤50 years old, male breast cancer, ovarian cancer, pancreatic cancer, or metastatic or high-risk prostate cancer
- Family history of at least three relatives with either breast or prostate cancer

Testing is done using a blood or saliva sample and usually screens for a panel of different gene mutations. The results provide complex information that should be reviewed with an experienced professional. Importantly, this information may also be relevant to other family members, as they may have inherited the same gene variants.[23]

Women without breast cancer who are found to have *BRCA1*, *BRCA2*, or some other germline mutations, have prevention options, including estrogen-blocking therapy (typically with tamoxifen or a related drug) or prophylactic surgery to remove the breasts (mastectomy). However, in a meta-analysis of data from 21 studies involving *BRCA* mutation carriers, risk-reducing mastectomy was found to lower breast cancer risk by 87%, but tamoxifen therapy did not significantly reduce risk.[24]

Staging

Prognostic staging has an important role in treatment decision-making. The American Joint Committee on Cancer

is responsible for developing cancer staging standards. Their most recent prognostic staging system, updated in 2018, takes into account the tumor's anatomical status (TNM classification), cellular features (histological grade), molecular biomarker (ER, PR, and HER2) status, and genomic profile.

TNM classification system

The tumor, node, metastasis (TNM) system is an anatomic staging system used to classify many types of cancer, including breast cancer. Combining the tumor's gross physical characteristics with data on outcomes allows for categorization into groups based on the predicted course of the disease and probable outcomes.[10]

TNM staging is based on information about tumor size and degree of invasion, whether the cancer has spread to lymph nodes on the same side of the body, and whether distant metastases are present.[10,25]

Table 3: Tumor, Node, Metastasis (TNM) Classification System[10,26]

Tumor Classification	Node Classification	Metastasis
Tx – Primary tumor cannot be assessed	Nx – Regional lymph nodes cannot be assessed	M0 – no clinical or radiographic evidence of distant metastases
T0 – No evidence of primary tumor	N0 – No lymph node metastases	M1 – distant metastases confirmed by clinical and radiographic means or histology
Tis – Carcinoma in situ (non- or pre-invasive)	N1 – Metastasis or micrometastasis involving 1–3 axillary (under the arm) lymph node(s)	
T1 – Tumor ≤20 mm in greatest dimension	N2 – Metastasis involving 4–9 axillary lymph nodes or any internal mammary (along the sternum) lymph nodes	
T2 – Tumor >20 mm but ≤50 mm in greatest dimension	N3 – Metastasis involving 10 or more axillary lymph nodes (or any in the group closest to the clavicle), a combination of axillary and internal mammary lymph nodes, or any supraclavicular (above the clavicle) lymph nodes	
T3 – Tumor >50 mm in greatest dimension		
T4 – Tumor of any size with direct extension to the chest wall and/or the skin		

Table 4: Breast Cancer Anatomic Stages

Stage	Definition
Stage 0	Tis, N0, M0
Stage I	IA: T1, N0, M0 IB: T0, N1(micro), M0 IB: T1, N1(micro), M0
Stage II	IIA: T0, N1, M0 IIA: T1, N0, M0 IIA: T2, N0, M0 IIB: T2, N1, M0 IIB: T3, N0, M0
Stage III	IIIA: T0, N2, M0 IIIA: T1, N2, M0 IIIA: T2, N2, M0 IIIA: T3, N1, M0 IIIA: T3, N2, M0 IIIB: T4, N0, M0 IIIB: T4, N1, M0 IIIB: T4, N2, M0 IIIC: any T, N3, M0
Stage IV	any T, any N, M1

In prognostic staging, these anatomic groupings are modified by information about grade, receptor status, and genomic profile when appropriate and available, which may result in upstaging (for example, in the case of TNBC) or downstaging (for example, in the case of triple receptor positivity: ER+, PR+, and HER2+).[25] For women who have not undergone breast cancer surgery, clinical prognostic staging is performed based on results of physical exam, imaging, and biopsy. Pathologic prognostic staging is based on findings from surgery, which provide a more accurate assessment of cancer status.[27]

Histologic grading

Histological grading is a standardized system for classifying tumors based on cellular characteristics. Tumor cells from biopsy samples are evaluated microscopically and scored based on the degree to which they have changed from normal functional cells. Those scores are then translated into three grades: grade 1 describes a tumor that is well-differentiated (has a high degree of normalcy) with little sign of cancerous change; grade 2 describes a moderately differentiated tumor with a moderate degree of abnormality or cancerous change; and grade 3 describes a poorly differentiated tumor with aggressive cancerous change.[22,25]

Molecular biomarkers and genomic profile

The presence or absence of the molecular biomarkers ER, PR, and HER2 have well-established implications for treatment responsiveness and breast cancer prognosis. Another protein biomarker called Ki-67 is an indicator of cell proliferation. High expression of Ki-67 has been correlated with more aggressive cancer; however, accurate

methods for assessing Ki-67 expression have yet to be standardized.[28]

Breast cancer can be categorized according to its molecular and genetic characteristics to better understand prognosis and guide treatment. Table 5 describes the main characteristics of the four molecular subtypes of breast cancer: luminal A, luminal B, HER2-positive, and triple negative. In addition, patterns of non-coding RNA (RNA fragments, such as microRNAs, that are not used for synthesizing proteins) have been associated with these subtypes. MicroRNAs are known to have a significant role in cancer cell function and may provide information about future therapeutic targets.[29]

Table 5: Characteristics of Molecular Subtypes of Breast Cancer[13]

	Luminal A	Luminal B	HER2-positive	Triple Negative
% of cases	~50	~15	~20	~15
ER-positive	yes	yes	sometimes	no
PR-positive	yes	sometimes	sometimes	no
HER2-positive	no	no	yes	no
Germline Mutations	—	BRCA2	—	BRCA1
Ki-67 expression	variable	variable	high	high
Prognosis	good	medium	medium to poor	poor
Systemic therapy options	endocrine therapy	endocrine therapy plus chemotherapy	endocrine, chemotherapy, and Herceptin	chemotherapy or immunotherapy

Genomic testing is used to detect gene mutations in tumor DNA. These mutations are not inherited but have been acquired since birth or arisen spontaneously in tumor cells. Tumor cells develop many gene mutations because they divide rapidly, and the tumor genomic profile is likely to change over time. Some of these mutations contribute to cancer cell aggressiveness and treatment resistance.[30,31]

Genomic profiling panels have been developed that can further individualize treatment decisions based on tumor gene patterns. For example, Oncotype DX is a multigene profiling test specifically used to predict risk of recurrence and the potential benefit of chemotherapy in patients with early-stage, ER-positive, HER2-negative (luminal A and luminal B subtypes) breast cancer. For patients with these breast cancer subtypes, the Oncotype DX score, if available, can be factored into prognostic staging and may be helpful for preventing over- and undertreatment.[25,32] Other genomic profiling panels include MammaPrint, Prosigna, and EndoPredict.[33]

Prognostic tools

A tool known as the Clinical Treatment Score post-5 years (CTS5) is used to evaluate the risk of distant recurrence in women with ER+ breast cancer who have completed five years of endocrine therapy. It is calculated using clinical information including patient age, tumor size, quadratic tumor size (tumor size squared [multiplied by itself]), node status, and histologic grade.[34,35] Another tool called the Breast Cancer Index (BCI) has been shown to predict which early-stage ER+ patients are likely to benefit from long-term (>5 years) endocrine therapy. It is calculated using genetic information from two tests.[33,36] CTS5 and BCI may be especially helpful for deciding whether to prolong endocrine therapy beyond five years in low- and intermediate-risk patients.[34,37,38]

3 Treatment

Overview

Breast cancer is a challenging diagnosis with treatment protocols that frequently involve multiple modalities, each with potential risks and possible benefits to be thoroughly considered and weighed by the patient and their care team. Good treatment decision-making takes into account a wide range of factors, such as stage and prognosis, previous treatments, possible side effects, length of treatment, and the patient's health.[14] In addition, it is vital to integrate patient values, preferences, and goals into treatment decision-making.[39]

Standard treatment options usually include some combination of surgery, radiation therapy, and systemic therapy (drugs that enter the bloodstream). Systemic therapy may consist of conventional chemotherapy with drugs that act generally to block cell replication, affecting cancer cells as well as other rapidly dividing cells in the body, or more targeted therapies, like endocrine therapy or immunotherapy (eg, anti-HER2 therapy), that take advantage of specific biomarkers and features of breast cancer cells to target and neutralize them. Patients may also be referred to participate in clinical trials of new treatments.[14]

Surgical Options

Most breast cancer patients undergo surgery to remove the tumor. The goals of surgery may include removal of the cancer, finding out whether the cancer has spread to lymph nodes or other tissues, restoring the shape of the breast after surgery, and relieving the symptoms of the cancer.[40] In some patients with small, low-grade DCIS tumors with a low risk of recurrence, surgery may be the only treatment needed.[11]

Lumpectomy vs. mastectomy

Depending on the characteristics of the tumor (eg, size, invasiveness, location), the patient may undergo removal of the tumor in a breast-conserving procedure called lumpectomy. This is also known as a partial mastectomy, segmental mastectomy, quadrantectomy, or breast-sparing surgery.[14,22] Lumpectomy also involves removal of some normal tissue around the tumor to provide a margin of confidence that all of the cancer has been removed. Narrow surgical margins are associated with increased risk of cancer recurrence, and a wider excision may be indicated for cases with aggressive features.[21,22]

Lumpectomy is often done in combination with radiation to reduce the risk of cancer recurrence. Studies have demonstrated this practice results in similar survival outcomes as removal of the whole breast (mastectomy) in women who have early-stage cancer and are candidates for either type of surgery.[40]

In some cases, it is necessary or preferable to remove the entire breast in a procedure called mastectomy. There are several types of mastectomy[22]:

- **Simple mastectomy**, in which the breast is removed but the chest muscles and axillary lymph nodes are spared
- **Skin-sparing mastectomy**, a variation of a simple mastectomy in which enough skin is left to cover the wound and potentially facilitate breast reconstruction
- **Nipple-sparing mastectomy**, like skin-sparing mastectomy, but the nipple and areola are spared for cosmetic reasons
- **Modified radical mastectomy**, in which some axillary lymph nodes are removed but the chest muscles are spared
- **Radical mastectomy**, in which the breast, chest muscles, and axillary lymph nodes are removed; used only in cases with invasion of the chest wall

Double or bilateral mastectomy, in which both breasts are removed, is sometimes performed when the risk of developing a second breast cancer is very high. Women with very high risk, such as those with *BRCA* gene variants, may opt for prophylactic bilateral mastectomy before a breast cancer diagnosis as a preventive measure.[22,40] Prophylactic mastectomy has been shown to reduce breast cancer risk by 87% in *BRCA* mutation carriers.[24]

Sentinel lymph node biopsy vs. axillary lymph node dissection

Lymphatic fluid leaving the breast tissue is mainly filtered by a large group of lymph nodes under the arm and

below the clavicle known as axillary lymph nodes. Because axillary lymph nodes are often the first site of breast cancer metastasis, their evaluation and monitoring are a critical part of breast cancer management.[3,26]

In most cases, ultrasound with biopsy is the first step in evaluating axillary lymph nodes. If spread to lymph nodes is absent or limited, this may be followed by sentinel node biopsy, in which a few critical nodes are removed and examined.[26,41] Sentinel lymph nodes are the first few lymph nodes to filter fluid from the tumor environment and are generally identified by injecting tracers near the tumor and seeing which lymph node or nodes receive them first.[41] In sentinel node biopsy, one or a few (usually two to four) sentinel nodes are identified and removed, often during partial or full mastectomy, and examined for the presence of cancer cells.[42] If no cancer is detected, no further axillary surgery is needed.[41]

Axillary lymph node dissection involves surgical removal of a large number of axillary lymph nodes. It may be offered if initial evaluation shows extensive node involvement or if cancer is found on sentinel node biopsy.[26,41] However, axillary lymph node dissection can cause side effects, such as edema (swelling due to fluid retention), limited arm movement, and nerve pain, which may have a substantial negative impact on quality of life. Radiation treatment to the axilla is an alternative to axillary lymph node dissection for some early breast cancer patients found to have cancer in one to two sentinel nodes and has been shown to result in similar survival outcomes.[41,42]

Reconstructive surgery options

Patients may choose to undergo breast reconstructive surgery at the time of initial breast surgery or later. Reconstructive surgery helps restore the breast's shape using the patient's own tissue (muscle, fat, and skin) or a breast implant. Reconstruction has been associated with better mental health and quality of life in patients who have undergone mastectomy. It is best to discuss reconstruction preferences early in treatment planning since timing may need to be coordinated around cancer treatments.[22,40,43]

A variety of factors affect whether breast reconstruction is appropriate, including patient preference, smoking, other medical conditions, and plans for radiation therapy. For example, smoking and obesity increase the risk of complications after breast reconstruction.[21] Women who do not choose reconstruction due to personal preferences, medical issues, or other factors can opt for a surgical closure that leaves a flattened chest wall, and may or may not want to use cosmetic external breast prostheses.[44]

Radiation Therapy

Indications and types

Radiation therapy involves using high-energy X-rays or other types of radiation to kill cancer cells.[14] In external beam radiation therapy, radiation is delivered by a machine from outside the body, while in brachytherapy or internal radiation, it is delivered under the skin by a needle, seed, wire, or catheter. The type and focus of the radiation therapy depends on the type of surgery (breast-conserving or mastectomy), involvement of lymph nodes, and individual patient and tumor factors, such as age, hormone receptor status, and preference.[40]

Radiation therapy is an important part of breast cancer treatment for many patients. It can reduce the chance of recurrence after breast-conserving surgery and may extend survival. Radiation is indicated after mastectomy in patients when the breast tumor is 5 cm or larger, when the cancer has spread to axillary lymph nodes, or when it is found to extend into surgical margins.[22] For patients whose breast cancer does not have these features, decisions around radiation therapy are made on a case-by-case basis.

A growing body of evidence indicates radiation therapy may be unnecessary for some women with early-stage ER-positive tumors who receive surgery followed by five years of endocrine (estrogen-blocking) therapy.[45,46]

There are many different dosing schedules and strategies for delivery of radiation therapy designed for different situations.[40] External beam radiation therapy is the more common mode of delivery and may be administered to the whole breast or the part of the breast closest to the tumor. It may also be applied to lymph nodes.[40] Brachytherapy may be an alternative to whole breast irradiation for some women who received breast-conserving surgery. The most common brachytherapy strategy in breast cancer is called intracavitary brachytherapy, in which a catheter is used to connect the outside of the breast to the cavity where the tumor was removed. The catheter is left in place, allowing radiation to be applied directly to the tumor area (usually twice per day for five days) until treatment is complete and the catheter is removed.[40]

Side effects

Radiation can cause a range of dose-related side effects by damaging healthy tissues near the tumor. The most common side effects of external beam radiation therapy are short-term and include breast swelling, skin changes similar to a sunburn, and fatigue. Long-term changes in breast texture and appearance and an inability to breastfeed may also occur. Axillary lymph node irradiation can cause chronic difficulty with edema in the arm or chest. In rare cases, radiation can damage ribs leading to weakness and fracture.[40]

Some women experience chronic numbness, pain, and weakness in the shoulder, arm, and hand due to radiation-induced nerve damage. The onset of these nerve problems can be many years after the end of treatment and may persist indefinitely.[47] Radiation can also cause scarring in the chest muscles, pleura (lining of the chest cavity), lung tissue, or heart muscle. With modern radiation techniques, these effects are less likely and less severe than in the past, but long-term health implications, such as increased cardiovascular risk in women treated for right-side breast cancer, have been noted.[48-50]

Brachytherapy is more invasive, but historically more targeted, than external beam radiation therapy and is associated with a somewhat different set of side effects. These include redness or bruising near the site of treatment, breast pain, infection, loss of fatty tissue in the breast, and pockets of fluid accumulation (seromas).[40] One advantage of brachytherapy is lower radiation exposure in nearby tissues and organs.[51] Nevertheless, brachytherapy has been found to cause rib weakness and fracture slightly more often than external beam radiation.[40,51,52]

Systemic Therapies

Systemic therapies encompass a wide variety of cancer therapies that are administered directly into the bloodstream intravenously or taken orally. They are called systemic because they reach the whole body, not just the breast. Systemic therapies used in breast cancer include general cancer-killing chemotherapies, endocrine therapies that target ERs, and other targeted therapies designed to take advantage of breast cancer-specific markers, such as the HER2 receptor.[40]

Systemic chemotherapy that is administered before surgery is called neoadjuvant chemotherapy. Neoadjuvant chemotherapy may be recommended for large tumors to reduce their size prior to surgery, for breast cancer involving many lymph nodes, and for inflammatory breast cancer. Systemic therapies administered after surgery to target residual cancer cells and reduce the risk of recurrence and spread are called adjuvant therapies.[40] In advanced and metastatic breast cancer, systemic therapies may be used to reduce further spread, relieve pain and other symptoms, extend life, and improve quality of life.[11] Decisions about which systemic therapies to use depend on the patient's cancer subtype and stage, genomic profile, and individual factors, including reproductive stage, health status, and personal preferences.[53-56]

Chemotherapy

Chemotherapy is indicated for many patients with invasive breast cancer that has spread to lymph nodes or other parts of the body. In patients with HR-positive, HER2-negative breast cancer, molecular testing may be used to decide whether chemotherapy is likely to be helpful. Chemotherapy is sometimes used prior to hormone therapy or with targeted therapy.[11]

Many chemotherapy agents used in breast cancer are the same as those used in other cancers. Agents used for neoadjuvant or adjuvant therapy include[11,40]:

- **Anthracyclines**, such as doxorubicin (Adriamycin) and epirubicin (Ellence), which inhibit DNA replication and generate free radicals that damage cancer cells
- **Taxanes**, such as paclitaxel (Taxol) and docetaxel (Taxotere), which interfere with cell division
- **Alkylating agents**, such as cyclophosphamide (Cytoxan) and carboplatin (Paraplatin), which interfere with normal DNA function
- **Fluoropyrimidines**, such as 5-fluorouracil (5-FU) and capecitabine (Xeloda), which interfere with DNA replication and repair

A number of other chemotherapy drugs may be used to treat breast cancer that has metastasized.[40]

By disrupting cell replication, these drugs exert their main toxic effects on cancer cells, which rely on rapid cell division. However, they can also harm healthy cells that divide rapidly, such as skin, hair, and bone marrow cells and the cells lining the digestive tract. This is why these medications cause side effects like hair loss, rashes, mouth sores, nausea and vomiting, diarrhea, and low white blood cell numbers.[11,14,40] Other possible side effects of chemotherapy include nail changes, loss of appetite, weight changes, fatigue, hot flashes, and nerve damage.[40] Some side effects are severe enough to limit treatment.

Although most side effects resolve after treatment is finished, serious long-term effects can occur following chemotherapy, including infertility, cardiomyopathy due to heart damage, neuropathy due to nerve damage, and diseases of the bone marrow, like leukemia. In some cases, these effects occur many years after the end of chemotherapy.[40]

Chemotherapy drugs are often used in combinations that take advantage of their different mechanisms of action. A variety of drug combinations are used, depending on tumor characteristics and individual patient factors.[33] They are administered in cycles separated by rest periods. The length of treatment is usually three to six months for neoadjuvant or adjuvant treatment, but can vary for metastatic disease.[40]

Endocrine therapy

Breast cancers that express high levels of estrogen and/or progesterone receptors depend on estrogen signaling to drive their growth. Endocrine (hormonal) therapies targeting estrogen signaling by blocking or breaking down ERs or by reducing synthesis of estrogen are widely used to interrupt cancer cell growth in ER-positive breast cancers.[40] Endocrine therapy is usually recommended as an adjuvant (post-surgery) therapy to prevent recurrence in patients with luminal-A or luminal-B breast cancer subtypes, as well as those with HER2-positive tumors that are ER-positive.[54] Emerging research suggests endocrine therapy targeting androgen receptors may improve outcomes in triple-negative breast cancer cases with high expression of androgen receptors.[57]

It is important to recognize that expression of progesterone receptors depends on estrogen signaling, and progesterone receptor activity modulates the activity of ERs. While progesterone receptors are an important, generally favorable, biomarker of prognosis in breast cancer, they are not directly targeted by endocrine therapies.[58] Endocrine therapy is sometimes recommended for those rare patients with ER-negative/PR-positive breast cancer, but its efficacy is uncertain.[54]

Endocrine therapies are associated with a host of side effects related to changes in estrogen signaling. These can include hot flashes, vaginal dryness, altered menstrual cycles, sexual dysfunction, mood difficulties, cognitive dysfunction, insomnia, fatigue, weight gain, and pain.[40,59] A substantial proportion of women report profound deterioration of quality of life during long-term endocrine therapy. Although these types of side effects diminish over time for some patients, they are a major reason for stopping therapy. Better support for patients taking long-term endocrine therapy may improve adherence, resulting in greater treatment benefits.[59,60]

Selective estrogen receptor modulators (SERMs)

Selective estrogen receptor modulators, or SERMs, block estrogen from binding to ERs. Tamoxifen (Nolvadex, Soltamox, et al.) is the most commonly used SERM and is used in both pre- and postmenopausal women with ER-positive breast cancer. Toremifene (Fareston) is also a SERM but is only approved for use in postmenopausal women with metastatic disease.[40]

The use of tamoxifen has been found to reduce risk of death by 25–31% and risk of recurrence by 41% annually. Five years of treatment has been shown to be more beneficial than one or two years, and 10 years of treatment has been found to improve outcomes even more for certain patients at high risk of recurrence.[22,54] Tamoxifen therapy is recommended for five years for patients with ER-positive DCIS and up to 10 years for patients with invasive ER-positive breast cancers. Considerations such as menopausal status, risk of recurrence, and adverse side effects are key to deciding how long to extend therapy for each individual patient.[11]

Common side effects of SERMs are related to reduced estrogen signaling and are listed above. In addition, SERMs affect estrogen signaling differently in different parts of the body, so can also cause certain pro-estrogenic side effects.[61] These include increased risk of endometrial cancer and uterine sarcoma in postmenopausal women as well as blood clots, such as deep vein thrombosis in the leg, which can progress to a

life-threatening pulmonary embolism. In rare cases, SERMs are associated with stroke. Their use has also been linked to eye problems, such as cataracts. SERMs may increase bone density in postmenopausal women but may decrease bone density in premenopausal women. It is important to note that the benefits of taking these drugs almost always outweigh the potential risks.[40]

Aromatase inhibitors

Aromatase is a key enzyme involved in the production of estrogen by cells outside of the ovaries, particularly fat cells. It facilitates the conversion of testosterone into estrogen, a pathway that accounts for a substantial proportion of estrogen synthesis in postmenopausal women. Aromatase inhibitors stop most non-ovarian estrogen production in the body and are an important option for long-term therapy in many cases of ER-positive breast cancer.[22,40]

In postmenopausal women, five to 10 years of aromatase inhibitor therapy can be used instead of tamoxifen. Alternatively, an aromatase inhibitor may be used before or following tamoxifen to achieve a total of up to 10 years of endocrine therapy. Aromatase inhibitors have demonstrated some outcome-related advantages over tamoxifen, but treatment decisions are sometimes influenced by side effects or treatment resistance. Because they do not affect ovarian estrogen synthesis, aromatase inhibitors are not effective in premenopausal breast cancer patients except in conjunction with ovarian suppression therapy.[11,54] Examples of aromatase inhibitors include letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin).

Side effects of aromatase inhibitors include the estrogen-depletion symptoms listed above, as well as muscle, bone, and joint pain that sometimes causes patients to discontinue treatment early. In such cases, switching to tamoxifen may be an option. Aromatase inhibitors also contribute to bone loss and increased fracture risk. This is sometimes managed with bone-protective medication.[40]

The optimal duration of aromatase inhibitor therapy has been the subject of several studies. In most cases, aromatase inhibitor therapy is recommended for at least five years and may be extended for as many as five more years. Prognostic tools, such as CTS5 or BCI, are useful for predicting the likely benefit of extending treatment.[34,36] Because the risk of side effects may outweigh additional benefits beyond years seven to eight, an individualized approach is important, weighing the potential benefit a patient may derive from extended aromatase inhibitor therapy against the potential for side effects, such as fractures.[62-66]

Selective estrogen receptor degraders (SERDs)

The selective estrogen receptor degraders (SERDs) fulvestrant (Faslodex) and elacestrant (Orserdu) are a newer class of drugs that interrupt estrogen signaling by binding to ERs and causing them to break down. These medications are used primarily in postmenopausal women but may be recommended in premenopausal women undergoing ovarian suppression therapy to medically induce menopause. Fulvestrant may be recommended instead of a SERM or aromatase inhibitor, or for patients whose ER-positive tumors have become resistant to another type of endocrine therapy.[40] It may also be used in combination with other systemic therapies for metastatic breast cancer. On the other hand, elacestrant is only approved for select patients with ER-positive/HER2-negative tumors that display a specific gene mutation (*ESR1*) associated with endocrine therapy resistance and have demonstrated resistance to one or more other endocrine therapies.[40,61]

In addition to hormonal side effects listed above, SERDs can be associated with nausea and pain in the muscles, joints, and bones. Elacestrant use has also been associated with increased cholesterol levels. Patients using fulvestrant, which is given by intramuscular injection, may experience pain at the injection site.[40]

Ovarian suppression

Ovarian suppression is used in conjunction with an aromatase inhibitor, or sometimes tamoxifen, to treat premenopausal women with ER-positive breast cancer and a high recurrence risk, such as due to young age, high-grade cancer, or lymph node involvement. Ovarian suppression plus tamoxifen or an aromatase inhibitor is generally recommended for five years, followed by up to five years of only tamoxifen, or an aromatase inhibitor if menopause has occurred during treatment.[54]

Luteinizing hormone-releasing hormone (LHRH) agonists such as goserelin (Zoladex) and leuprolide (Lupron) disrupt normal feedback signaling between the ovaries and the brain, dramatically decreasing ovarian estrogen

production and inducing temporary menopause. Alternatively, some women opt for surgical removal of the ovaries, leading to permanent menopause. In some cases, chemotherapy damages ovarian function and induces menopause as a side effect, which may be temporary or permanent. Ovarian suppression results in the estrogen-depletion symptoms common to all endocrine therapies.[40]

Targeted therapy

The promise of personalized cancer care depends largely on targeted treatment options. This is an area of active research as molecular targets are discovered and new agents directed at them are developed.

HER2-targeting antibodies

Monoclonal antibodies that target HER2, including trastuzumab (Herceptin), pertuzumab (Perjeta), and margetuximab (Margenza), are used to treat patients with HER2-positive breast cancer. These drugs are administered intravenously and may be used alone or in combination with chemotherapy, as well as endocrine therapy when indicated, for early or advanced-stage breast cancer.[40]

HER2-positive breast cancer patients undergoing adjuvant (post-surgery) chemotherapy are generally co-treated with trastuzumab. This is followed by trastuzumab alone, once every three weeks, for up to one year. Trastuzumab can also be part of neoadjuvant (pre-surgery) treatment for large tumors or those with substantial node involvement.[11,40,54] Combining trastuzumab with pertuzumab may slightly improve outcomes in high-risk cases.[11,22,54] Margetuximab use is typically limited to advanced breast cancer cases that have not responded to other HER2-targeted therapies.[40]

The most serious side effect of trastuzumab is cardiac damage. While cardiotoxic effects of trastuzumab usually cause no symptoms and are reversible after therapy ends, it has been associated with life-threatening congestive heart failure in rare cases.[67] The risk of lasting heart damage is compounded in patients who also receive cardiotoxic chemotherapy, such as anthracycline, paclitaxel, or cyclophosphamide.[68,69] Trastuzumab is not safe in pregnancy.[40] Other potential side effects include respiratory problems, diarrhea, indigestion, sleep difficulty, hot flashes, peripheral neuropathy (numbness, tingling, or burning sensation in the hands, feet, arms, or legs), and pain in the joints, muscles, or bones.[69]

Antibody-drug conjugates are another HER2-targeting treatment option. They are made by attaching HER2-targeting monoclonal antibodies, such as trastuzumab, to chemotherapy drugs. This allows the HER2-targeting antibody to deliver the chemotherapy drug directly to cancer cells. Antibody-drug conjugates include trastuzumab-emtansine (Kadcyla) and trastuzumab-deruxtecan (Enhertu). They are generally reserved for use in cases of advanced metastatic breast cancer that have progressed despite first-line treatment with trastuzumab plus chemotherapy,[40] although trastuzumab-emtansine is also used in certain cases of early-stage breast cancer.[70]

In an important clinical trial, trastuzumab-deruxtecan improved treatment outcomes in breast cancer patients whose tumor expression of HER2 was just below the threshold needed to be classified as HER2-positive and were therefore classified as HER2-low.[71] This led to the 2024 Food and Drug Administration (FDA) approval of trastuzumab-deruxtecan for advanced HER2-low breast cancer, regardless of hormone receptor status.[61]

Common side effects of trastuzumab-drug conjugates include nausea, decreased appetite, fatigue, and headache. These medications can also cause lung, liver, and bone marrow toxicity.[72]

Kinase inhibitors

Kinase inhibitors are a broad class of drugs that inhibit enzymes called kinases. Kinases activate a range of cellular processes, including metabolism, signaling, growth, and division. Kinase inhibitors are widely used in cancer treatment, including breast cancer.

Tyrosine kinase inhibitors. HER2 is a type of enzyme called a tyrosine kinase, and some tyrosine kinase inhibitors (TKIs) have been shown to inhibit HER2. These include lapatinib (Tykerb), neratinib (Nerlynx), and tucatinib (Tukysa).[40,68] Tyrosine kinase inhibitors have been shown to improve outcomes in advanced or metastatic HER2-positive breast cancer patients who have stopped responding to trastuzumab. Clinical trials have indicated these TKIs help restore sensitivity to trastuzumab; therefore, TKIs and trastuzumab are often used together even after resistance to trastuzumab has been displayed. They are generally used along with chemotherapy, as well as endocrine therapy when appropriate. In some cases of early-stage breast cancer,

neratinib may also be recommended. Common side effects of TKIs include diarrhea, nausea, vomiting, and rash.[68] Some TKIs can also cause hand-foot syndrome, marked by soreness, redness, blistering, and peeling of the hands and feet.[40]

CDK4/6 inhibitors. These oral medications target cyclin-dependent kinases (CDKs) 4 and 6, which, like other CDKs, play a critical role in controlling the cell division cycle. Rapidly dividing breast cancer cells are particularly vulnerable to CDK4/6 inhibitors.[73]

Palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio) are CDK4/6 inhibitors used in breast cancer treatment. Multiple clinical trials over the past decade have found that these drugs slow progression and promote stability when added to endocrine therapy in patients with advanced or metastatic HR-positive/HER2-negative breast cancer.[74] More recently, several important trials have investigated their potential benefits when used as part of adjuvant therapy in patients with early breast cancer deemed high-risk due to large size, high-grade, or significant lymph node involvement.[54,75]

A randomized controlled trial in 5,637 high-risk early breast cancer patients found abemaciclib combined with endocrine therapy increased the likelihood of invasive disease-free survival from 76% to 83.6% and distant relapse-free survival from 79.2% to 86% after a median of 54 months of monitoring.[76] Another randomized controlled trial compared ribociclib plus endocrine therapy to endocrine therapy alone in 5,101 patients with HR-positive/HER2-negative stage II or III breast cancer. After a median of 34 months, invasive disease-free survival was higher in the ribociclib group (90.4%) than no-ribociclib group (87.1%).[77] Although monitoring is ongoing, as of late 2025, neither drug has demonstrated a significant benefit to overall survival in this patient group.[75] These findings prompted a change to treatment guidelines in 2024 recommending the use of abemaciclib or ribociclib as part of adjuvant therapy in patients with early but high-risk HR-positive/HER2-negative breast cancer.[33,78]

On the other hand, two large trials were unable to show adding palbociclib to adjuvant therapy affected survival outcomes in high-risk HR-positive/HER2-negative breast cancer patients without metastatic disease.[79,80]

CDK4/6 inhibitors can cause low blood cell numbers, leading to increased risk of serious infections. They are also associated with rare but life-threatening inflammation of the lungs. Other possible side effects include fatigue, diarrhea, hair loss, mouth sores, nausea and vomiting, and headache.[40]

PI3K/AKT/mTOR inhibitors. The phosphatidyl-inositol-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway controls cell metabolism, growth, proliferation, and survival. Cancer growth depends on dysregulated activation of the PI3K/AKT/mTOR pathway, and therapies that target inhibition may be helpful in cancer treatment.[81]

Everolimus (Afinitor) is an mTOR inhibitor that was shown to improve the effectiveness of the aromatase inhibitor exemestane in patients with HR-positive/HER2-negative advanced breast cancer that progressed or recurred despite aromatase inhibitor therapy. It was the first PI3K/AKT/mTOR inhibitor to be approved by the FDA for breast cancer treatment in 2012. Several severe adverse events have been associated with everolimus, including mouth sores, anemia, shortness of breath, high blood glucose levels, fatigue, and lung inflammation.[81]

About 30–40% of breast cancer patients with HR-positive tumors have a mutation in the *PIK3CA* gene that makes PI3K overactive, promoting proliferation and contributing to treatment resistance. The PI3K inhibitor alpelisib (Piqray), in combination with the SERD fulvestrant, was shown to improve outcomes in patients with breast cancer that was HR-positive/HER2-negative and carried the *PIK3CA* mutation. This finding led to the 2019 FDA approval of alpelisib, in combination with fulvestrant, for treating breast cancer with these characteristics that has progressed or recurred despite endocrine therapy.[40,81,82] The most common severe adverse effects associated with alpelisib were high blood glucose levels, rash, and diarrhea.[81]

Some breast cancer patients have an *AKT1* mutation that dysregulates AKT activity and is associated with endocrine therapy resistance. The AKT inhibitor capivasertib (Truqap) was found to improve the response to fulvestrant in select breast cancer patients.[83] Based on this evidence, in 2023, the FDA approved capivasertib for use in combination with fulvestrant to treat patients with HR-positive/HER2-negative advanced or metastatic breast cancer that displays one or more *AKT1*, *PIK3CA*, or *PTEN* mutations and has stopped responding to endocrine therapy.[84] Severe side effects include high blood pressure, diarrhea, and rash. There may also be an increased risk of severe respiratory infection in patients taking capivasertib.[81]

A number of novel PI3K/AKT/mTOR inhibitors, including dual inhibitors, are currently under investigation for their potential role in treating advanced or metastatic, HR-positive, HER2-negative breast cancer. In addition, new methods of testing for PI3K/AKT/mTOR abnormalities are being explored.[81]

PARP inhibitors

Poly (ADP ribose) polymerase (PARP) inhibitors suppress the activity of a family of DNA repair enzymes called PARP proteins. Cancer cells divide rapidly and generate many DNA errors, making them especially vulnerable to PARP inhibitors. PARP inhibitors appear to be more effective in breast cancer patients who have inherited *BRCA* mutations, which also compromise DNA repair. Olaparib (Lynparza) and talazoparib (Talzenna) are PARP inhibitors that are approved for use as stand-alone treatment in patients with advanced or metastatic breast cancer who carry an inherited *BRCA* mutation.[40,61]

Olaparib is also approved for treatment of *BRCA*-associated HER2-negative breast cancer with a high risk of recurrence. This is based on evidence showing one year of adjuvant olaparib increased distant disease-free survival and invasive disease-free survival after four years in patients with BRCA mutations and high-risk HR-positive/HER2-negative breast cancer. In addition, four-year overall survival was increased from 86.4% with placebo to 89.8% with olaparib.[85] It can be used alongside endocrine therapy and before or after abemaciclib if appropriate.[33]

These medications are associated with side effects, including nausea and vomiting, diarrhea, loss of appetite, weight loss, fatigue, bone marrow suppression resulting in low blood cell and platelet numbers, and, in rare cases, bone marrow cancer.[40]

Immunotherapy

Immunotherapies enhance the immune system's ability to detect and kill cancer cells. Monoclonal antibodies that target HER2 are an example of an immunotherapy (and a targeted therapy). Checkpoint inhibitors, another class of immunotherapy drugs used in cancer treatment, prevent cancer cells from "turning off" immune T cells and evading recognition.[40] While breast cancer has historically been thought to be unresponsive to checkpoint inhibitor therapy, new research has indicated these drugs may be an effective option when combined with chemotherapy in select patients.[86]

Pembrolizumab (Keytruda) is currently the only checkpoint inhibitor approved for treating triple-negative breast cancer. It has been shown to improve outcomes when used with neoadjuvant (pre-surgery) and adjuvant (post-surgery) chemotherapy in patients with early-stage, high-risk, triple-negative breast cancer and when used with chemotherapy in previously untreated patients with advanced or metastatic triple-negative breast cancer whose tumors express high levels of the checkpoint protein PD-L1.[86-88]

In a randomized controlled trial involving 1,174 patients with stage II or III triple-negative breast cancer, the rate of event-free survival (defined as survival without disease progression, recurrence, occurrence of a second primary cancer, or death from any cause) was higher in those treated before and after surgery with combinations of chemotherapy plus pembrolizumab (84.5%) compared with chemotherapy plus placebo (76.8%).[87] In other words, pembrolizumab lowered the relative risk of recurrence, progression, or death by 37%.[86] Further analysis of the data indicated pembrolizumab was effective in patients with tumors that were PD-L1-positive or PD-L1-negative.[87]

Another trial compared pembrolizumab plus chemotherapy to placebo plus chemotherapy in 847 patients with untreated advanced triple-negative breast cancer expressing PD-L1. After a median follow-up of 44.1 months in patients with the highest levels of PD-L1 expression, overall survival was 23.0 months with pembrolizumab and 16.1 months with placebo. However, in those with lower PD-L1 expression, overall survival was not improved with pembrolizumab compared with placebo (17.6 vs. 16.0 months).[88]

Side effects of pembrolizumab include fatigue, cough, nausea, skin rash, poor appetite, constipation, and diarrhea. Some people experience allergy-like infusion reactions, which can be severe, while receiving pembrolizumab, which is administered intravenously.[40] By disabling the immune system's ability to regulate T cells, checkpoint inhibitors can also cause autoimmunity that may be severe or, in rare cases, life-threatening.[86]

Maintaining Bone Health During and After Breast Cancer Treatment

Bone disorders, such as osteoporosis, are common in those who have undergone breast cancer treatment.[89] The relationship between breast cancer and bone loss is due in part to the multifaceted role of estrogen and the effect of various cancer therapies on estrogen metabolism. While estrogen is a driver of the disease process in a large percentage of breast cancer cases, estrogen is also a needed regulator of bone growth and remodeling.[90]

Most breast cancer patients are women in their postmenopausal years, a life stage in which estrogen production is low and bone density is already diminished.[91,92] In addition, certain breast cancer treatments can aggravate bone loss and increase the risks of osteoporosis and fracture in both pre- and postmenopausal women.[92] These include[92,93]:

- Aromatase inhibitors, which interrupt estrogen synthesis
- Corticosteroids, which impair bone cell function
- Some chemotherapy agents, which can cause toxic injury to ovaries and bone cells
- Surgical ovary removal or other treatments that suppress ovarian function, which induce early menopause in younger breast cancer patients

In addition to these effects, breast cancer treatments can contribute to muscle loss and dysfunction, reducing the ability to perform bone-protective physical activity and disrupting two-way signaling between muscle and bone that is necessary for musculoskeletal health.[89]

Aromatase inhibitors in particular have significant musculoskeletal toxicity, causing such side effects as muscle and joint pain, weakness, tendinopathies, bone loss, and increased fracture risk.[89,94] Their use has been associated with damaging effects on bone density as well as bone microarchitecture, reducing bone quality.[95-97] Some preclinical research has found that increased bone turnover and altered bone microarchitecture due to aromatase inhibitor use can stimulate growth factor release and activation in the bone matrix and possibly contribute to the growth of breast cancer metastases in bone.[89] Interestingly, a study in 372 early breast cancer patients treated with aromatase inhibitors for five to 10 years found bone loss slowed or was partially reversed during years five through 10 in those who stopped therapy at year five.[98]

Selective estrogen receptor modulators (SERMs) (eg, tamoxifen) have a more nuanced effect on bone. By blocking estrogen, tamoxifen worsens bone loss in premenopausal (ie, estrogen-replete) breast cancer patients. However, because of its slight estrogen-like effect on bone tissue, tamoxifen increases bone density and reduces fracture risk in postmenopausal (ie, estrogen-deficient) women.[90,93]

Risk factors for bone loss

In addition to certain breast cancer therapies, factors that increase the risk of bone loss in breast cancer patients include[99]:

- Older age
- Female sex
- Asian or white ethnicity
- History of a previous fracture
- Family history of osteoporosis
- Smoking
- Heavy alcohol use
- Inadequate exercise
- Low body weight
- Low calcium intake
- Vitamin D deficiency
- Pre-existing low bone mineral density
- Certain chronic medical conditions or long-term use of certain medications (eg, glucocorticoids)

Screening guidelines

International guidelines, including those of the American Society of Clinical Oncology, recommend breast cancer patients being treated with aromatase inhibitors undergo fracture risk assessment before starting

treatment and periodically throughout adjuvant hormone therapy. This includes screening for risk factors (listed above) and measuring bone mineral density (BMD).[100,101] Observational research has shown breast cancer survivors who underwent baseline BMD screening before starting aromatase inhibitor therapy were more likely to receive appropriate medication to treat bone loss and had a lower risk of fractures.[102,103]

Dual-energy X-ray absorptiometry (DXA) is the standard test for assessing BMD. It is used to detect osteopenia and osteoporosis, monitor treatment, and as part of a fracture risk assessment.[100,104] The result of a DXA scan is reported as a T-score, which compares a patient's BMD to that of a healthy young person. In general, a T-score of –2.5 or lower is diagnostic of osteoporosis; however, not all individuals with a high fracture risk have a low T-score. In fact, some evidence shows that DXA-determined bone density can be normal or only slightly below normal even in patients in whom vertebral fractures have been detected.[100]

The Fracture Risk Assessment Tool, or FRAX, is an online tool that estimates 10-year fracture risk based on variables that include age, body weight status, personal and family history of fracture, BMD, and other factors related to osteoporosis and fracture risk. Importantly, like DXA scanning, FRAX was not designed specifically for breast cancer patients and may not be equipped to accurately reflect fracture risk in the context of breast cancer.[91,100]

Bone strength depends not only on bone density but also bone quality. Trabecular bone score is an emerging technology to assess the microarchitecture of trabecular bone (the spongy inner bone region) as a reflection of bone quality. The score is based on specialized examination of the image from a DXA scan.[105] By providing information about bone quality, trabecular bone score may help detect increased fracture risk in breast cancer survivors who received aromatase inhibitors, even in cases with unchanged BMD.[100,106] Another test, called three-dimensional high-resolution peripheral quantitative computed tomography (pQCT), evaluates BMD through volumetric measurement and assesses the microstructure of both trabecular and cortical bone regions. High-resolution pQCT has been used to provide novel insights into changes in bone geometry, mass, quality, and strength that may affect fracture risk in women treated with aromatase inhibitors.[95,96] Future research is needed to establish the usefulness of these and other methods and to develop related treatment guidelines in breast cancer patients.[107]

While bone imaging technologies are the standard means of objectively evaluating bone status, blood and urine biomarkers of bone remodeling may provide information about the rate of bone loss and help with monitoring effectiveness of therapy. They include markers of bone breakdown, such as urinary N-telopeptide and serum C-telopeptide, and markers of bone formation, such as bone-specific alkaline phosphatase, osteocalcin, and serum amino-terminal propeptide of type 1 procollagen (PINP).[104] Though not generally used to assess fracture risk, bone biomarker tests may be helpful for detecting accelerated bone loss due to breast cancer treatment.[100,104] They are usually performed under the supervision of an endocrinologist or other bone health expert.

Treatment of osteoporosis in breast cancer patients

Breast cancer treatment-induced bone loss is treated with pharmacologic bone-modifying agents. Diet and lifestyle measures and targeted nutrient supplementation can play an important supportive role but, in this context, are insufficient as a stand-alone approach.[100]

Bone-modifying agents

According to a 2017 joint position statement issued by seven international cancer and bone societies, bone-modifying agents should be initiated in women with breast cancer receiving aromatase inhibitors whose T-scores are < –2.0, those with T-scores < –1.5 plus one additional risk factor, and those with two or more risk factors.[108] Risk factors identified for the purpose of this recommendation included:

- Age ≥ 65 years
- Current or past smoker
- Body mass index (BMI) < 20 kg/m ^{2}
- Family history of hip fracture
- Personal history of fragility fracture after 50 years of age
- Glucocorticoid therapy for longer than six months

Bisphosphonates, a class of drugs that inhibit bone breakdown, are first-line therapy for osteoporosis. Oral bisphosphonates, including alendronate (Fosamax), risedronate (Actonel), and ibandronate (Boniva), have been demonstrated to improve BMD in postmenopausal women with early-stage breast cancer treated with aromatase inhibitors.[91,109] Zoledronic acid (Reclast or Zometa) is a bisphosphonate that is administered by intravenous infusions, typically every six to 12 months. It has been shown to improve BMD in pre- and postmenopausal women with early-stage breast cancer receiving chemotherapy or hormone-targeting therapies.[91]

In addition to slowing bone loss, the use of bisphosphonates has been shown to improve breast cancer-related outcomes in high-risk postmenopausal (but not premenopausal) women.[110,111] A meta-analysis of data from 17 randomized controlled trials and eight observational studies involving a total of 81,508 participants found bisphosphonate therapy reduced the risk of bone metastases and improved survival in early-stage postmenopausal breast cancer patients.[112] Nevertheless, the effect of bisphosphonate therapy on fracture risk in these patients is still uncertain.[109]

Bisphosphonates are associated with two rare but serious potential side effects: atypical femur fracture and osteonecrosis of the jaw. The likelihood of experiencing a major adverse side effect is increased with long-term use (3–5 years or longer). The vast majority of cases of jaw osteonecrosis are in cancer patients.[91,104] A randomized controlled trial in 211 women with early-stage breast cancer found those who received a single infusion of zoledronic acid had fewer side effects and similar bone benefits and survival, compared with those who received multiple infusions at six-month intervals after three years.[113]

Denosumab (Prolia) is a monoclonal antibody that inhibits bone breakdown by targeting receptor activator of nuclear factor kappa-B ligand (RANKL), a protein that upregulates activity of osteoclasts (cells responsible for bone breakdown). Denosumab is administered by subcutaneous injections, typically at six-month intervals.[114] It has been shown to increase BMD and prevent fractures in women taking aromatase inhibitors.[115]

In a randomized placebo-controlled trial called D-CARE that included 4,509 chemotherapy-treated women with early-stage breast cancer, denosumab was found to reduce fracture risk similarly in both pre- and postmenopausal participants.[116]

The most serious adverse side effect of denosumab is osteonecrosis of the jaw, which has been reported in more than 2% of cancer patients receiving high-dose denosumab. It has also been associated with rare instances of atypical femur fracture.[104] A correlational study in 780 patients found previous use of a bisphosphonate and having a dental procedure prior to or during denosumab therapy were factors associated with increased risk of osteonecrosis of the jaw.[117] Because rapid bone loss occurs after stopping denosumab, follow-up therapy with zoledronic acid is recommended.[91]

Although the evidence for fracture prevention in breast cancer patients is stronger with denosumab than bisphosphonates, there are conflicting results regarding denosumab's possible survival benefits.[91,118] In a randomized placebo-controlled trial, 3,425 postmenopausal women with early-stage breast cancer who received aromatase inhibitor therapy were given denosumab at 60 mg subcutaneously every six months, or placebo. After a median follow-up of eight years, the denosumab group had lower risk (in absolute terms) of several outcomes than the placebo group: 3.5% lower rate of breast cancer recurrence, 2.5% lower rate of bone metastasis, and 1% lower risk of death from any cause.[119] Conversely, in the D-CARE trial (described above), 120 mg of subcutaneous denosumab administered every three to four weeks for about six months and then every 12 weeks for five years did not improve bone metastasis or recurrence rates compared with placebo.[120] More research is needed to determine whether denosumab has survival benefits and to establish the optimal dose and schedule for breast cancer patients.

Outcomes for denosumab and zoledronic acid treatment were compared and analyzed in a cohort of 864 breast cancer patients with HR-positive/HER2-negative advanced breast cancer with bone metastases. All patients were receiving CDK4/6 inhibitors plus endocrine therapy. Bone-related events and survival were assessed. No differences in survival outcomes were noted, but zoledronic acid treatment resulted in a longer time until the occurrence of bone-related incidents.[121]

Calcium and vitamin D

Many breast cancer patients have low or deficient vitamin D levels.[122] One study that included 636 Chinese women with a new diagnosis of breast cancer found 92.3% had vitamin D deficiency or insufficiency and 15.3% had low calcium levels. In addition, breast cancer patients were 5.5 times more likely to have osteopenia and 3.4 times more likely to have osteoporosis, even before initiating cancer treatment, than matched women without breast cancer.[123] The National Comprehensive Cancer Network recommends young breast cancer patients at risk of bone loss and women over age 50 years get 1,200 mg of calcium per day and supplement with 20–25 mcg (800–1000 IU) of vitamin D daily.[99,100]

In an observational study, 210 postmenopausal early-stage breast cancer patients receiving aromatase inhibitors were enrolled in a comprehensive bone health program that included vitamin D supplementation, exercise, counseling, and intravenous bisphosphonate therapy as needed. After one year, most of those with baseline osteopenia or osteoporosis had stable or improved BMD.[124]

A trial without a control group that included 82 breast cancer patients receiving an aromatase inhibitor found adding 1,000 mg of calcium plus 50–100 mcg (2,000–4,000 IU) of vitamin D3 daily for 12 weeks improved calcium and vitamin D status and decreased medication-induced joint pain.[125] In an open-label, randomized, controlled trial involving 41 breast cancer patients, 45 mcg of calcitriol (Rocaltrol, a prescription form of fully activated vitamin D) per day for 12 weeks improved levels of bone-specific alkaline phosphatase, a marker of bone formation.[126] Because high doses of calcitriol can potentially cause toxic effects by elevating blood calcium levels, it should only be used with supervision.[127]

Emerging Research and Clinical Trials

Novel treatments

New treatments are constantly being developed and tested in all stages of breast cancer. Treatment paradigms are changing as new targets are discovered and existing treatments are shown to work in new settings, combinations, and schedules. For example, agents that target androgen receptors, which may be overexpressed by triple-negative, and possibly ER-negative/HER2-positive, breast cancer cells, are an active area of endocrine therapy research.[128] Novel antibody-drug conjugates, new drugs targeting established markers like ERs, HER2, and checkpoint proteins, and drugs with new targets like HER3, other kinases, and other immune-regulating molecules are among the many approaches under investigation.[129-131]

The wide field of immunotherapy is one of the most promising areas of breast cancer treatment research. For example, ongoing research is investigating new ways of combining checkpoint inhibitors with other therapies, such as antibody-drug conjugates, chemotherapy, or endocrine therapy in breast cancer patients.[132-134] Immunotherapy drugs targeting two or more tumor molecules (bispecific antibodies) are a field of emerging clinical research.[131,132] Another intriguing potential therapy is adoptive cell therapy, in which a patient's T cells are collected, modified in the laboratory to combat cancer cells more aggressively, and returned to the bloodstream.[131,132] Challenges associated with these approaches include immune dysregulation and the development of serious autoimmune side effects, as well as tumor cell adaptation and treatment resistance.[132]

Cancer vaccines, which activate immune cells to recognize and kill cancer cells, are another field of active research with potential for use in breast cancer treatment and recurrence prevention. Cancer vaccines have a better side-effect profile than other immunotherapies, but so far have not shown strong benefits.[131,132] Some research indicates a role for anti-cancer vaccines in augmenting the effects of other targeted therapies.[131]

Oncolytic (cancer-killing) viruses, which preferentially infect cancer cells, can directly kill tumor cells, as well as make them easier for immune cells to detect and kill. Clinical trials are being designed to investigate the effects of adding oncolytic virus therapy to various breast cancer treatment protocols.[131,132] Cytokines like interferon are up-regulators of immune function and are being explored for their potential role in directing immune activity against breast cancer cells.[131]

Optimizing radiation therapy is another area of emerging research. Studies are focusing on: establishing markers to identify women who will not be harmed by omitting radiation therapy; finding optimal strategies for minimizing damage to healthy tissue; and developing safer ways of delivering more potent radiation therapy when needed or re-irradiating a breast in cases of recurrence.[135]

How to participate in clinical trials

Clinical trials are an essential part of improving cancer care and depend on the willingness of individuals to participate. Clinical trials test the safety and efficacy of new treatments or treatment combinations in breast cancer or may be designed to test questions regarding other aspects of care. By supporting research, volunteer participants help further the evidence base and may improve breast cancer treatment for others. They may also benefit personally from test treatments.[136] Breast cancer trials generally test new treatments against standard treatments, so all participants receive appropriate care.[137]

As of early 2025, there were more than 900 clinical trials in breast cancer listed on the National Cancer Institute's clinical trials website. Each trial is testing a specific question in a certain well-defined category of breast cancer patients. If you are interested in being a part of a clinical trial, find out if you are eligible and explore the possibilities with your provider. More information about clinical trials in breast cancer can be found at the National Cancer Institute's **Participate in Cancer Research** website.

Personalized Treatment Approaches

Personalized breast cancer care involves tailoring treatment to a range of patient characteristics, such as age, menopausal status, and health, as well as personal preferences. For example, while certain therapies may not be suitable for some older breast cancer patients, evidence shows patients in good overall physical health can benefit from aggressive cancer treatments even at an older age.[138] Menopausal status is another important factor in choosing effective treatment.[21] In addition, the potential impact of therapeutic choices on fertility may influence preferences.[56] Patients who have *BRCA*mutations may choose to take preventive measures, such as prophylactic endocrine therapy or mastectomy, without a cancer diagnosis.[139]

Cancer profiling

Biomarkers are used as indicators of an individual's prognosis and probable treatment response. In breast cancer, established biomarkers include ER, PR, and HER2. In addition, detecting genetic changes associated with breast cancer can further refine treatment to target the specific vulnerabilities of each patient's tumor. Modern genomic profiling tools can provide patient-specific information about tumor gene activity and may be useful in guiding treatment choices, predicting treatment resistance, and measuring treatment response. These types of tumor analyses are the basis of precision medicine.[140-142]

Genomic profiling panels have been developed that can test the activity level or expression of a number of genes at the same time, allowing for the detection of gene patterns associated with certain tumor behaviors. These tests are meant to complement the information gathered for staging and subtyping of breast cancer.[21]

Two widely available genomic profiling tests for breast cancer are the Oncotype DX and MammaPrint panels.

- **Oncotype DX** is recognized by the National Comprehensive Cancer Network and American Society for Clinical Oncology as useful for prognosis and prediction of chemotherapy benefit in early-stage patients with ER-positive/HER2-negative invasive breast cancer. It tests the expression of 21 different genes to categorize the risk of recurrence as low, intermediate, or high.[21,143] A number of studies have shown this test can improve treatment decision-making with regard to adjuvant (after surgery) endocrine or chemotherapy treatments.[143]
- **MammaPrint** tests expression of 70 different genes and can be of value for guiding decisions regarding adjuvant endocrine therapy and chemotherapy in early-stage ER-positive/HER2-negative breast cancer patients who are postmenopausal or over age 50.[143] It categorizes the risk of recurrence as high or low.[21]

Other genomic profiling panels, including **EndoPredict**, **Prosigna**, Immunohistochemistry 4 (IHC4), and Breast Cancer Index (BCI), are also available for use in ER-positive/HER2-negative breast cancer patients; however, they are not as well studied as Oncotype DX and MammaPrint.[143] Another similar test, **FoundationOne Liquid CDx**, is FDA approved as a companion diagnostic tool to help guide targeted treatment selection in patients with metastatic breast cancer. It assesses PIK3CA, AKT, and ESR1 gene mutation status among others. Of interest, the BCI was recently shown to predict which patients would benefit from extended endocrine therapy.[36]

Liquid biopsy

Liquid biopsy is an emerging diagnostic and monitoring procedure that identifies circulating cancer cells or their components in blood samples or sometimes other body fluid samples (such as urine and saliva). Currently, liquid biopsies for breast cancer are performed using blood samples. Liquid biopsies play a role in individualized treatment decision-making through detection and analysis of:

- **Circulating tumor cells.** The presence of tumor cells in the bloodstream may indicate residual cancer after treatment or may be an early sign of recurrence or metastasis. The molecular and genetic characteristics of these cells may help guide therapy. Their propensity to form clusters and their interactions with immune cells provide more information that could be useful in personalizing treatment and directing future research.[144-146]
- **Circulating tumor DNA.** DNA from dying cancer cells may be found in the blood and can be examined for highly specific markers that can be helpful in making individualized treatment decisions. Repeat testing for circulating tumor DNA may be useful as a dynamic marker of treatment response and can inform treatment decisions.[144,146]
- **Tumor microRNA.** Tumor microRNA and other cellular components may be useful as prognostic biomarkers and in the development of new targeted therapies.[146]

The future of personalized medicine in breast cancer

Active areas of research in breast cancer include identifying new biomarkers to guide therapy, predict treatment response, and detect treatment resistance as it emerges. The search for these markers takes advantage of new technologies that allow for rapid analysis of tumor protein and genetic information. For example, mutations in a tumor gene called *ESR1* affect estrogen receptor expression and are associated with resistance to endocrine therapy and sensitivity to SERDs, such as elacestrant. Using tumor DNA, detection of these mutations may help guide treatment choice for a patient who has had a recurrence while on an endocrine therapy.[140,142] Next-generation sequencing of tumor DNA obtained through tissue biopsies, as well as circulating tumor cells, DNA, and RNA retrieved through liquid biopsies, may result in better detection of DNA changes that may be targetable by new or known treatments.[141]

4 Dietary and Lifestyle Considerations

Being physically active, adhering to a healthy diet, and maintaining a healthy body weight are important parts of a holistic approach to breast cancer treatment. These factors influence treatment tolerance, recovery during and after cancer treatment, and outcomes. Therefore, diet and exercise during and after cancer treatment should be discussed between patients and their care team as soon as possible after breast cancer diagnosis.[147]

Adherence to the recommendations encompassed in the American Heart Association's ***Life's Essential 8*** could be beneficial for breast cancer survivors.[148] *Life's Essential 8* are as follows:

1. Eat better
2. Be more active
3. Quit tobacco
4. Get healthy sleep
5. Manage weight
6. Control cholesterol
7. Manage blood sugar
8. Manage blood pressure

The following are general recommendations from the American Cancer Society[147,149]:

- Practice healthy weight management strategies and maintain or increase muscle mass through diet and physical activity.
- Engage in physical activity for a minimum of 10 minutes per day several times per week if possible.
- Build up to 150–300 minutes of moderate-intensity or 75–150 minutes of vigorous activity each week and include resistance training and stretching exercises at least twice per week.

- Follow a healthy eating pattern that includes nutrient-dense foods, such as vegetables, legumes, whole grains, and nuts and seeds, and limits red and processed meats, sugar-sweetened beverages, highly processed foods, refined grains, and alcohol.

Healthy Diet

A healthy diet that aligns with such dietary patterns as the Mediterranean diet has been shown to reduce the risk of developing breast cancer and may improve breast cancer-related outcomes. Such a diet is high in fruits and vegetables, healthy fats, unrefined grains, beans, nuts and seeds, and fish, and low in red and processed meat, refined grains, and added sugars.[150] A meta-analysis of findings from 35 observational studies and 14 clinical trials showed healthy high-quality diets reduced overall mortality by 23% compared with unhealthy low-quality diets in breast cancer patients.[151] Another meta-analysis pooled findings from four observational studies and found strong adherence to a Mediterranean diet was correlated with a 22% lower risk of all-cause mortality in breast cancer survivors.[152] The positive effects of healthy eating on breast cancer outcomes may be due to beneficial modulation of the gut microbiome, inflammatory signaling, and anti-proliferative pathways, as well as other mechanisms that affect cancer cell growth.[150]

Other dietary regimens, such as modified fasting, calorie restriction, vegan/plant-based diets, and ketogenic diets, are being investigated in breast cancer patients. For example, a systematic review found intermittent fasting (the practice of not eating for long periods, often roughly 16–48 hours, followed by regular eating) may reduce chemotherapy-induced toxicity, and some research suggests it may lower the recurrence rate in breast cancer patients.[153,154] A ketogenic diet, characterized by very low carbohydrate and high fat intake, has attracted interest for its potential role in cancer treatment. It is thought to target cancer cells due to their metabolic dependence on glucose, whereas healthy cells can utilize fat metabolites (ketones) as a primary energy source. Some evidence suggests a ketogenic diet may improve treatment responsiveness in breast cancer patients. However, clarity around its role in treatment and concerns about long-term safety remain unresolved.[155] Studies examining the benefits of plant foods and plant-based diets have indicated higher intakes of fruits, vegetables, fiber, and soy foods (such as tofu, tempeh, miso, and edamame) may improve breast cancer outcomes.[156] Importantly, following a healthy plant-based diet (high in fruits, vegetables, and whole grains) has been linked to lower overall mortality, while an unhealthy plant-based diet (low in fruits and vegetables and high in refined grains) has been correlated with increased mortality in breast cancer patients.[156]

Physical Activity

Exercise during cancer treatment is safe and there is strong evidence that physical activity before and after diagnosis can reduce the risk of mortality for breast cancer patients. It is also clear that physical activity may reduce the risk of developing cancer in both pre- and postmenopausal women, may reduce the risk of cancer recurrence, and can help cancer survivors cope with and recover from therapy. Exercise programs should be personalized for each patient and tailored to their clinical situation.[150,157]

A meta-analysis of 24 studies including more than 140,000 participants analyzed the effects of physical activity on breast cancer outcomes and found between 300 and 500 minutes (5 to 8.3 hours) per week of moderate-intensity physical activity improved prognosis and reduced mortality.[158] Another meta-analysis of 23 observational studies concluded that about five hours per week of moderate recreational physical activity was associated with a 48% reduction in all-cause mortality and 38% lower breast cancer specific mortality, with minimal additional risk reduction associated with higher levels of physical activity.[157]

Two Cochrane analyses concluded that structured exercise is safe and beneficial for women with breast cancer, but the two studies looked at different periods during breast cancer treatment.[159,160] **During adjuvant therapy** (chemotherapy and/or radiation), programs typically ran 6–32 weeks (some up to 52), often 2–5 sessions per week for about 30–60 minutes, and produced a moderate boost in physical fitness and a small-to-moderate reduction in fatigue; effects on overall cancer-specific quality of life and depression were minimal.[159] **After adjuvant therapy**, aerobic training was most often 3–5 days per week for 30–90 minutes at about 40–80% of maximal heart rate, and resistance training approximately 2–5 days per week for 30–60 minutes at roughly 65–85% of one-repetition maximum over about 8–24 weeks; these regimens yielded small improvements in fatigue, moderate gains in cardiorespiratory fitness, and modest, variable benefits across quality-of-life domains.[160]

Across both reviews, the most consistent outcome was improved physical fitness, with fatigue reduction as a close second, while quality-of-life changes were smaller.

Managing fatigue and enhancing recovery

Physical activity may help a patient feel better before treatment and recover more quickly after treatment both physically and mentally. It can also help with sleep, depression, and other mental health challenges that are common with cancer treatment.[149,161]

Cancer-related fatigue—a feeling of physical, mental, and emotional exhaustion from cancer therapy, the cancer itself, and other cancer-related issues, such as sleep problems—may be alleviated in part by physical activity.[161,162] In coordination with the patient's care team, a physical activity program for overcoming cancer-related fatigue might start out with 10 minutes at a time of exercise or stretching and gradually increase as the patient is able.[149,161] Authors of a 2025 meta-analysis on the effects of exercise during and after breast cancer treatment concluded that low-to-moderate-intensity exercise is recommended during treatment, and that moderate-to-high-intensity exercise can be beneficial after treatment.[162]

Stress Management and Mental Health

Breast cancer and its treatment can be emotionally and physically demanding, and most patients experience some feelings of anxiety, depression, and distress. Mental health support can contribute to better quality of life for both patients and their loved ones. Mental health support may include stress reduction practices, counseling, education, spiritual support, and group support from a variety of health and counseling professionals.[163]

Managing stress

Breast cancer patients can experience multiple sources of stress, including the seriousness of the condition, treatments and decision-making, fear of recurrence, economic concerns, changes in body image and sexuality, and concerns for family and friends.[164]

A meta-analysis that evaluated data from 24 randomized controlled trials with a total of 1,187 participants found non-drug interventions, such as yoga, self-regulation, mindfulness, and physical activity, can reduce feelings of stress, anxiety, and depression in breast cancer patients.[164] Physical exercise, including aerobic activities and resistance training, has been shown to help patients manage treatment-related anxiety, fatigue, depression, and sleep difficulties.[147,149] In addition, mindfulness and relaxation techniques can improve a patient's ability to adhere to healthy eating regimens while also reducing stress, anxiety, and depression. Mindfulness refers to a practice of slowing down and focusing on the present using breath awareness, guided imagery, body relaxation, and other techniques. Examples of some of these techniques can be found **here**.[165]

Support groups and counseling

Peer support groups bring together people with similarities to share experiences, fears, and concerns. These may be people who have the same type of cancer, are getting the same type of treatment, or have other circumstances in common. They may be led by a facilitator who is a healthcare professional or a cancer survivor. Peer support can create a mutual therapeutic and emotional connection and facilitate an educational and supportive patient-centered journey.[166] Being comfortable with the approach and structure of the group and feeling safe and respected are key to benefitting from peer support groups.[163]

Individual counseling can also be helpful for those who have been diagnosed with breast cancer. This allows the patient to focus on their personal concerns and situation with a mental health professional. Individual counseling may be useful for managing fears, coping with life changes, handling family issues, and discussing concerns about body image and sexuality in a private setting. Counseling may also be useful for couples or families as they navigate cancer care together.[163]

Cognitive behavioral therapy (CBT) in particular has been shown to improve mental health in breast cancer patients. Cognitive behavioral therapy is a technique for identifying and changing unhelpful thoughts and behaviors to improve emotional well-being. One meta-analysis that pooled findings from 16 interventional studies investigating CBT as individual or group therapy found it reduced anxiety and depression in both breast cancer patients and survivors.[167] A growing body of evidence indicates internet-based CBT can also improve depression, anxiety, and quality of life in breast cancer patients.[168]

5 Nutrients

Specific nutrients and dietary supplement ingredients have been investigated for their possible role as part of breast cancer treatment, either to reduce risk of recurrence, prolong survival, or reduce toxic side effects from other treatments. While a number of dietary supplements have shown potential to modify breast cancer risk, general prevention is outside the scope of this protocol. We have limited inclusion of nutrients in this section to those for which there is some clinical evidence in the context of breast cancer treatment (including post-treatment).

Antioxidant Combinations

Antioxidants are members of a broad category of nutrients and other compounds that can donate electrons, effectively neutralizing free radicals and protecting against oxidative damage. Dietary antioxidants are likely to be an important reason some foods, like fruits and vegetables, are linked to lower cancer risk. However, the use of antioxidant supplements during cancer treatment is controversial. Because chemotherapy and radiation kill cancer cells largely by inducing oxidative damage, concerns about antioxidants reducing their effectiveness have been raised. On the other hand, antioxidants protect and repair non-cancerous cells and tissues, possibly making cytotoxic treatments more tolerable and augmenting their effectiveness.[169]

A meta-analysis of eight observational studies that included a total of 17,062 breast cancer patients found post-diagnosis use of antioxidant supplements, defined as supplements containing vitamins A, C, and/or E, sometimes in combination with other nutrients, was not associated with any significant change in survival outcomes. However, the analysis noted older studies were more likely to find benefits associated with antioxidant use, while more recent studies were more likely to find harms.[170] For example, one observational study in which 1,134 breast cancer patients answered questions about supplement use before and during chemotherapy found the use of any antioxidants, specifically vitamins A, C, or E, carotenoids, or CoQ10, before or during treatment was associated with higher recurrence rate and slightly lower survival rate six months after starting treatment.[171] Nevertheless, another meta-analysis of observational studies and clinical trials found the use of certain antioxidant supplements (vitamins C and E) or multi-nutrient supplements after diagnosis was associated with lower risk of recurrence and mortality.[172]

Melatonin

Reported dosage: 3–20 mg nightly

Melatonin, a hormone produced mainly in the pineal gland in the brain,[173] is a regulator of circadian signaling throughout the body. Melatonin has demonstrated a range of positive effects on broad health indicators that may be beneficial in cancer therapy: it reduces oxidative stress, suppresses inflammatory processes, preserves mitochondrial function, improves metabolism, and supports normal cell function.[174,175] Furthermore, preclinical studies in breast cancer models suggest melatonin reduces tumor growth factor production, modulates expression of estrogen and progesterone receptors as well as HER2, and suppresses tumor kinase signalling.[176]

Research from the 1990s reported melatonin had positive effects on breast cancer treatment. A controlled clinical trial in 250 patients with metastatic solid tumors, including 77 with breast cancer, reported supplementing with 20 mg melatonin nightly reduced chemotherapy toxicity and improved one-year survival rate (51% with melatonin vs. 23% without melatonin).[177] The same research team conducted a trial that had no control group and found melatonin, at 20 mg nightly, improved responsiveness to endocrine therapy in 14 metastatic breast cancer patients.[178]

More recent trials have shown melatonin may have benefits for specific parameters of sleep, cognition, and mood during breast cancer treatment. A randomized placebo-controlled trial involving 48 women undergoing surgery for breast cancer found 6 mg of melatonin nightly, beginning three days before and continuing for one to two weeks after surgery, increased sleep efficiency (the proportion of time in bed spent sleeping) and reduced wakefulness after sleep onset.[179] In another placebo-controlled trial with 43 participants, 6 mg of melatonin nightly beginning one week before breast cancer surgery and continuing for three months reduced the risk of depressive symptoms.[180] A randomized controlled trial in 36 breast cancer patients found 20 mg of melatonin nightly, beginning three days before and for one week during the first cycle of adjuvant chemotherapy, improved cognitive performance compared with placebo, and the effect was associated with increased sleep quality and decreased

depressive symptoms.[181]

A randomized placebo-controlled trial in 74 breast cancer patients found 18 mg of melatonin nightly, taken from one week before until one month after completing adjuvant chemotherapy and radiation, improved fatigue scores and reduced the frequency of severe fatigue.[182] A longer trial conducted by the same research group included 92 breast cancer patients who received either 18 mg of melatonin per day or placebo for two years following adjuvant therapies. At the end of the trial, those given melatonin were still experiencing less fatigue than those given placebo.[183] A trial with no control group that involved patients with metastatic breast cancer undergoing endocrine or trastuzumab therapy found 5 mg of melatonin nightly for two months improved sleep quality and quantity, as well as fatigue, quality of life, and social and cognitive functioning.[184] A randomized placebo-controlled trial in 86 postmenopausal breast cancer survivors no longer in active treatment found 3 mg of melatonin nightly for four months improved sleep quality.[185] On the other hand, a trial in 78 early-stage breast cancer patients compared 20 mg of melatonin per day to placebo, taken from one day before until two weeks after completing radiation therapy, and found melatonin had no effect on fatigue or other parameters.[186] Similarly, a retrospective registry study involving analysis of data from over 37,000 breast cancer patients showed that having been prescribed melatonin for about three months or more was not associated with improved survival.[187]

Topical Melatonin Protects Skin During Radiotherapy

Topical melatonin may protect the skin during radiation therapy. Two reports from a randomized placebo-controlled trial in 48 breast cancer patients undergoing radiation therapy compared a placebo cream to 1 gram of skin cream containing 25 mg of melatonin plus 150 mg of dimethyl sulfoxide (DMSO). The melatonin/DMSO cream, applied twice daily on irradiated skin during and for two to three weeks after radiation therapy, increased the likelihood of having a low score on a skin side effects of radiation scale and lowered overall breast symptom scores compared with placebo during radiation, but these differences had diminished by two weeks after the end of radiation.[188,189] Similarly, a placebo-controlled trial in 47 breast cancer patients found that applying a melatonin emulsion to irradiated breast skin twice daily during and for two weeks after radiation therapy significantly reduced the occurrence of radiation dermatitis.[190]

Omega-3 Polyunsaturated Fatty Acids

Reported dosage: About 1–1.8 grams omega-3 fatty acids (EPA and/or DHA) daily; this generally was obtained from about 2–5.8 grams of fish oil or 4.5 grams of algae oil daily

The long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are abundant in oily fish and often obtained in the form of fish oil supplements. They have well-established anti-inflammatory and immune-modulating effects, and higher intake of these fatty acids has been linked to lower breast cancer risk in observational research.[191-193]

One clinical trial with no control group examined the effect of 1.8 grams of DHA (from 4.5 grams of algae oil) daily on outcomes during an average of 31 months of monitoring in patients who received anthracycline-based chemotherapy for rapidly progressing metastatic breast cancer. The researchers found patients who attained the highest DHA plasma levels progressed more slowly and had longer survival times than those who attained lower levels. Those who achieved high plasma DHA levels had a median time to progression of 8.7 months and overall survival of 34 months, while those who did not had a median time to progression of 3.5 months and overall survival of 18 months. DHA supplementation was not associated with any adverse effects. This finding suggests DHA may sensitize malignant tumors to chemotherapy.[194]

In a randomized controlled trial involving 48 patients with locally advanced breast cancer, 1 gram of omega-3 fatty acids from fish oil daily during 51 days of neoadjuvant chemotherapy reduced tumor tissue levels of the proliferation marker Ki-67 and vascular endothelial growth factor (VEGF, a protein involved in tumor blood vessel formation). In addition, fish oil extended cancer-free and overall survival compared with placebo: average survival was 30.9 weeks with fish oil and 25.9 weeks with placebo.[195]

Supplementing with omega-3 fatty acids can improve general health, including cardiovascular and metabolic status, and this may improve overall outcomes in breast cancer. A controlled trial in 32 breast cancer patients

found 4 grams of fish oil daily (providing 800 mg EPA and 400 mg DHA) for 60 days beginning at the start of chemotherapy increased chest muscle strength and improved cardiorespiratory fitness.[196] Another trial in 51 subjects with HR-negative breast cancer found omega-3 fatty acid supplementation for one year reduced triglyceride levels and led to epigenetic changes favoring healthy lipid metabolism. The trial also showed a roughly 5.8-gram (3.7 gram EPA and 1.6 gram DHA) daily dose had stronger effects than a 1-gram (670 mg EPA and 240 mg DHA) daily dose.[197] A randomized controlled trial in 88 newly diagnosed breast cancer patients found 600 mg of omega-3 fatty acids (providing 360 mg EPA and 240 mg DHA) daily plus 1,250 mcg (50,000 IU) of vitamin D weekly for nine weeks during the initiation of chemotherapy improved global health and functioning scores and reduced markers of inflammation compared to vitamin D or fish oil alone or to no supplements.[198] However, a trial in 53 women with non-metastatic advanced breast cancer found no cardiometabolic benefit from supplementing with 2.4 grams of omega-3 fatty acids (providing 1,600 mg EPA and 800 mg DHA) daily during neoadjuvant chemotherapy.[199]

Some evidence suggests omega-3 fatty acids may improve immune function and tumor-suppressive immune activity in breast cancer patients. In a randomized controlled trial, breast cancer patients received either 2 grams of fish oil (providing 1.8 grams of omega-3 fatty acids) daily or a mineral oil placebo for 30 days after diagnosis and before surgery. At the end of the trial, those given fish oil had reduced levels of high-sensitivity C-reactive protein (hsCRP, a marker of inflammation) and higher levels of immune-activating CD4+ T cells (T4 cells), while those given mineral oil had increased hsCRP and decreased T4 cell levels.[200]

Musculoskeletal pain is a common side effect of aromatase inhibitors, affecting approximately 45–60% of patients, particularly those with obesity. In fact, pain is a major cause of treatment discontinuation.[94]

The chemotherapy agent paclitaxel frequently causes peripheral neuropathy (ie, numbness in the hands and feet). In a randomized controlled trial, 57 breast cancer patients being treated with paclitaxel took either 640 mg of omega-3 fatty acids (including 346 mg DHA and 64 mg EPA) three times daily or placebo during and for one month following paclitaxel therapy. Those treated with omega-3 fatty acids were about half as likely to experience peripheral neuropathy.[201] However, in a randomized placebo-controlled trial in 49 patients, 4 grams of a pharmaceutical formulation providing ethyl esters of EPA (about 1,900 mg) and DHA (about 1,500 mg) per day from one week before beginning paclitaxel, until the end of paclitaxel treatment, did not reduce treatment-induced neuropathy.[202]

Vitamin D

Reported dosage: Approximately 50 mcg–175 mcg (2,000 IU–7,000 IU) daily

Vitamin D is a steroid hormone that regulates calcium metabolism, modulates immune activity, and promotes normal cell replication. It is synthesized in the body in response to sunlight, is found in foods such as fatty fish, eggs, mushrooms, and fortified dairy products, and is often taken as a supplement. Some studies, though not all, have found a high prevalence of vitamin D deficiency (generally defined as serum 25-hydroxyvitamin D levels < 20 ng/mL) and insufficiency (generally defined as 25-hydroxyvitamin D levels below 30 ng/mL) among newly diagnosed breast cancer patients, particularly those with triple negative breast cancer, suggesting poor vitamin D status may be a contributing factor in its onset.[191,203,204]

Vitamin D deficiency in breast cancer patients has been correlated with poorer response to neoadjuvant chemotherapy and a higher risk of breast cancer mortality.[205,206] One meta-analysis of 12 studies with a total of 8,574 participants found those with the highest vitamin D levels, compared to those with the lowest vitamin D levels, had a 26% relative increase in overall survival, 50% increase in disease-free survival, and 31% increase in breast cancer-specific survival.[206] Another meta-analysis included six studies in which surgical samples from a total of 1,291 breast cancer patients treated with neoadjuvant chemotherapy were analyzed for treatment responsiveness. The pooled results showed that pretreatment 25-hydroxyvitamin D levels < 20 ng/mL were associated with a 50% increased risk of a pathologic non-complete response (meaning residual invasive cancer cells were detected) and a 33% increase in risk of no response (meaning invasive disease persisted after treatment).[205]

In a randomized controlled trial conducted in Brazil, 75 women undergoing neoadjuvant chemotherapy for breast cancer received 50 mcg (2,000 IU) of supplemental vitamin D3 daily or placebo for six months. Both groups were

found to have low blood vitamin D levels at the beginning of the trial. Vitamin D levels improved in the vitamin D3 group and 43% achieved a pathologic complete response (defined as the absence of invasive disease in breast and lymph nodes), whereas vitamin D levels were stable in the placebo group and only 24% achieved a pathologic complete response.[207] Another randomized clinical trial examined outcomes in 227 women with breast cancer, age 18 to 80 years, undergoing neoadjuvant chemotherapy. Half the women received 1,250 mcg (50,000 IU) of oral vitamin D once per week during neoadjuvant chemotherapy while the other half did not. Over 70% of trial participants, in both groups, had either deficient (<20 ng/mL) or insufficient (20–30 ng/mL) vitamin D levels at baseline, which improved in the supplementation group. In addition, the pathologic complete response rate was 2.3 times higher in those who received vitamin D.[208]

Vitamin D has demonstrated other effects that suggest it may be helpful in breast cancer treatment. In a randomized placebo-controlled trial in 44 breast cancer patients being treated with tamoxifen, 1,250 mcg (50,000 IU) of vitamin D weekly for eight weeks reduced levels of an indicator of blood vessel formation and tumor growth (angiopoietin-2) more than placebo in a subgroup composed of premenopausal participants whose cancer had not infiltrated blood or lymph vessels.[209] Findings from a nine-week, randomized, controlled trial in 88 newly diagnosed breast cancer patients indicated a combination of vitamin D (1,250 mcg [50,000 IU weekly]) plus omega-3 fatty acids (600 mg daily) may be more effective than either alone for lowering inflammation, reducing treatment side effects, and improving nutritional status and overall health and functioning during chemotherapy.[198,210]

Vitamin C

Reported dosage: 500 mg orally per day. *Note:* ≥ 1 gram per kg of body weight of intravenously administered vitamin C two to four times per week has also been reported, but this dosage approach requires medical supervision.

Vitamin C, or ascorbic acid, is abundant in fruits and vegetables and is important for immune health and protecting cells from free radicals.[191] Vitamin C has well known free radical-scavenging and anti-inflammatory properties. Preclinical research has also demonstrated that it has the ability to inhibit abnormal cell proliferation, suppress expression of proteins involved in cell transformation, and at high concentrations can raise oxidative stress in tumor cells.[211] In addition, meta-analyses of observational studies have found post-diagnosis vitamin C supplementation was associated with a 16–21% reduction in relative risk of overall mortality.[170,172,212]

Some clinical data support a benefit of vitamin C for reducing adverse treatment effects in breast cancer patients. A randomized controlled trial in 40 early-stage breast cancer patients found 500 mg of vitamin C, along with 400 IU of vitamin E (as alpha tocopherol acetate), during chemotherapy mitigated the reduction in antioxidant enzyme levels, rise in oxidative stress, and DNA damage caused by chemotherapy and cancer.[213] Whether these effects could translate into protection against side effects or improved outcomes is not yet known.

Because intestinal absorption of vitamin C is limited, intravenous administration can be used to achieve higher blood levels. One observational study examined data from 424 breast cancer patients treated with adjuvant radiation therapy, 70 of whom were co-treated with intravenous vitamin C twice weekly for at least four weeks. Those who received intravenous vitamin C at ≤1 gram/kg body weight or did not receive vitamin C had an increase in the neutrophil-to-lymphocyte ratio—a change in immune cell proportions that reflects inflammation and is correlated with increased overall and breast cancer-specific mortality. However, those who received intravenous vitamin C at >1 gram/kg body weight experienced a decrease in this ratio.[214]

Another observational study found 35 triple-negative breast cancer patients who received intravenous vitamin C at 1 gram/kg body weight, beginning three days before and continuing every other day during one full cycle of chemotherapy, had fewer adverse side effects and longer progression-free and overall survival than 35 matched patients who received chemotherapy alone. In those who received vitamin C, average progression-free survival was seven months and overall survival was 27 months, while in those who did not receive vitamin C, average progression-free survival was 4.5 months and overall survival was 18 months.[215] This equates to a 56% relative increase in progression-free survival and a 50% relative increase in overall survival. An observational study compared data from 53 patients with non-metastasized invasive breast cancer who received 7.5 grams of intravenous vitamin C once weekly for at least four weeks during standard treatment and 72 similar patients who

did not receive vitamin C. Those who received vitamin C had fewer chemotherapy and radiation therapy side effects such as nausea, loss of appetite, fatigue, depression, sleep disorders, dizziness, and bruising/bleeding disorders than those who did not.[216]

Vitamin E

Reported dosage: 400 IU–1,300 IU (approximately 180 mg–600 mg) daily

Vitamin E is a fat-soluble antioxidant nutrient found in fatty foods, such as nuts, seeds, avocados, olives, and plant oils. In breast cancer cell studies and animal models of breast cancer, vitamin E has been shown to suppress tumor growth and proliferation, promote cell death, enhance tumor suppressor gene activity, and improve immune function.[217]

In an open-label, randomized, controlled trial in 31 cancer patients, 600 mg of vitamin E daily during and for three months after completing chemotherapy resulted in a 66% reduction in neuropathy.[218] This dose was equivalent to about 900–1,300 IU per day, depending on the type of vitamin E used (not specified in the publication). In a randomized controlled trial involving 74 breast cancer patients, a combination of 400 IU (180 mg) vitamin E plus carnitine during four cycles of chemotherapy with doxorubicin plus cyclophosphamide resulted in a 24.2% relative reduction in cardiac events compared with chemotherapy alone. The form of vitamin E used in this study was dl-alpha-tocopherol.[219] A meta-analysis of findings from nine studies also indicated vitamin E supplementation may reduce the risk of breast cancer recurrence.[220] In addition, one randomized controlled trial found combination treatment with 400 IU (about 270 mg) of vitamin E as alpha-tocopherol per day plus pentoxifylline (Trental, a drug that improves blood flow) for six months following radiation therapy reduced radiation-related scarring in the breast and chest wall, though it had no effect on survival during two years of monitoring.[221]

Green Tea

Reported dosage: 940 mg–1,200 mg oral EGCG daily; 600 micromol/L (about 275 mg/L) EGCG spray used topically during radiation therapy

Consumption of green tea may reduce the risk of developing breast cancer and may improve outcomes after breast cancer diagnosis.[191,222] The protective effects of green tea have been attributed to bioactive polyphenolic compounds called catechins, the most abundant of which is epigallocatechin-3-gallate (EGCG). Catechins have numerous modulating effects on cellular pathways known to be involved in cancer.[191,223,224]

One small study provided preliminary evidence that cancer-related pathways may be affected by consumption of supplemental EGCG in breast cancer patients. Molecular markers on surgical tissue samples from 13 women with early-stage breast cancer waiting for surgery who took 2,175 mg green tea extract, containing about 940 mg EGCG, per day (roughly equivalent to 8–10 cups of green tea) for an average of 35 days prior to surgery were compared with those from 15 matched breast cancer patients who received no green tea. The women in the green tea extract group had lower levels of the proliferation marker Ki-67 in both benign and malignant cells compared with the control group.[225]

There is also some evidence that green tea can impact the risk of breast cancer recurrence. An observational study that monitored 518 women with triple-negative breast cancer for a median of 9.1 years found those who reported drinking green tea regularly during the five years after diagnosis were 46% less likely to have a recurrence compared with those who did not drink green tea.[226] A meta-analysis of seven observational studies involving a total of 13,956 women with a breast cancer diagnosis found those who drank the most green tea (generally 3–8 cups per day) had a 19% lower likelihood of recurrence.[224]

Green tea may have particular benefits for breast cancer patients being treated with radiation therapy. In a small, randomized, placebo-controlled trial involving 10 women with metastatic breast cancer undergoing radiotherapy, 400 mg of EGCG three times daily during therapy reduced blood levels of growth factors and enzyme activity related to cancer growth compared with placebo.[227] Findings from preliminary clinical trials suggest an EGCG-containing topical formula (600 micromol/L EGCG spray) may alleviate radiation-induced dermatitis when applied to the skin of breast cancer patients undergoing radiation therapy.[228,229]

Curcumin

Reported dosage: 6,000 mg of standard curcumin orally per day or 300 mg intravenously per week

***Dosage note**: Some curcumin formulations have been shown to increase absorption and thus may achieve blood levels comparable to higher-dose unformulated curcumin. The studies described here used an unformulated curcumin preparation so this dosage range should not be confused with a dosage range for enhanced-absorption curcumin formulations. Also, curcumin should not be administered intravenously without qualified medical supervision.*

Curcumin is a polyphenolic compound extracted from turmeric. In laboratory studies, curcumin has been found to slow proliferation of breast cancer cells, cause tumor cells to die, and prevent tumors from developing blood vessels to supply nutrients.[191]

A preliminary dose-finding case series included nine patients with advanced metastatic breast cancer receiving chemotherapy with docetaxel once every three weeks for five or six cycles. They received oral curcumin at doses of 500 mg to 8,000 mg per day for seven days during each three-week cycle, timed to include four days before, the day of, and two days after chemotherapy. Three patients achieved stable disease and five had a partial response six or more weeks after their last cycle of docetaxel. However, two participants experienced diarrhea and one experienced low white blood cell numbers, which may have been related to curcumin. The study authors determined 6,000 mg daily was a safe oral dose for future research.[230] In a randomized, double-blind, placebo-controlled trial involving 30 breast cancer patients, 2,000 mg of oral curcumin three times daily during radiation treatment reduced the severity of radiation dermatitis: average radiation dermatitis scores, based on a 0–4.0 scale, were 2.6 in the curcumin group and 3.4 in the placebo group at the end of radiation therapy.[231] This equates to a 24% relative reduction in radiation dermatitis scores with curcumin. The curcumin preparation used in the study was a branded standardized curcumin extract called Curcumin C3 Complex.

High oral doses of curcumin are sometimes used in trials due to low absorption of standard curcumin preparations. Intravenous curcumin has been explored as an alternative in some trials.[232] In a randomized controlled trial, 150 patients with progressive, advanced, or metastatic breast cancer received paclitaxel plus 300 mg of intravenous curcumin or placebo weekly for 12 weeks. The curcumin group had a higher overall response rate than the placebo group (51% vs. 33%) four weeks after the end of treatment, but the difference had diminished (29% vs. 20%) by 12 weeks after the treatment period. The curcumin group also reported less fatigue and better physical performance, suggesting better treatment tolerance.[233]

Coenzyme Q10

Reported dosage: 100 mg daily

Coenzyme Q10 (CoQ10) is an antioxidant involved in cellular energy production. Muscle tissues, including heart muscle, have a high requirement for CoQ10.

Observational evidence suggests low CoQ10 levels are associated with breast cancer risk and with expression of genetic biomarkers related to tumor growth.[234,235] Other observational studies and case descriptions have reported CoQ10, in combination with essential fatty acids and other antioxidants (eg, vitamin C, vitamin E, selenium, folic acid, and beta-carotene), extended survival time beyond median predicted survival (based on patient demographics and tumor characteristics and stage) in advanced and metastatic breast cancer patients.[236-238]

CoQ10 has been shown to reduce fatigue in healthy people and those with chronic conditions, but to date there is little evidence of benefit for cancer-related fatigue.[239] A randomized controlled trial in 57 breast cancer patients with cancer-related fatigue undergoing chemotherapy found a combination supplement providing 30 mg of CoQ10 plus amino acids, minerals, and B vitamins once daily for 21 days reduced the most severe fatigue levels and global fatigue scores, but did not change average fatigue levels or quality of life scores.[240] Another randomized placebo-controlled trial in 236 breast cancer patients found no improvement in fatigue, mood, or quality of life after 24 weeks of supplementing with 100 mg of CoQ10 plus 100 IU of vitamin E daily.[241]

In a meta-analysis of findings from nine randomized controlled trials in breast cancer survivors who had received tamoxifen for at least six months, 100 mg of CoQ10 per day for 45–90 days decreased levels of VEGF (needed for tumor blood vessel formation), interleukin-8 (IL-8, an inflammatory cytokine), and matrix metalloproteinases (proteins involved in tumor cell growth and proliferation), but did not alter markers of inflammation and oxidative stress.[242] Whether or not these effects of CoQ10 could lead to better treatment outcomes is not known.

Sulforaphane and Indole-3-carbinol

Reported dosage: Approximately 35 mg sulforaphane *or* 300 mg diindolylmethane (DIM) daily

Numerous observational studies have indicated high consumption of cruciferous vegetables (eg, broccoli, kale, cabbage, Brussels sprouts) is associated with a lower risk of a range of cancers, including breast cancer.[243] Sulforaphane is a sulfur-containing phytochemical from cruciferous vegetables that has been shown in preclinical research to have anti-inflammatory and anti-cancer properties. Unfortunately, clinical research investigating its potential role in breast cancer treatment is sparse.[244]

In a preliminary randomized controlled trial, 30 newly diagnosed postmenopausal breast cancer patients received broccoli sprout extract containing 200 micromoles (about 35 mg) of sulfur compounds (including sulforaphane) or placebo daily for two weeks prior to surgery. The dose of broccoli sprout extract was equivalent to about 500 grams (more than one pound) of fresh broccoli. Tissue samples at the beginning and end of the trial showed markers of cancerous activity were not statistically different between the two groups.[245] A trial ongoing as of late of 2025 is evaluating the potential for supplemental sulforaphane to reduce chemotherapy-induced cardiac dysfunction.[246]

Indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM) are other sulfur compounds found in crucifers. Preclinical and clinical evidence suggests I3C and DIM have multiple anti-cancer actions. Among them, these compounds have been shown to shift estrogen metabolism toward production of non-toxic and potentially anti-cancer byproducts, and may thereby help protect against hormone-dependent breast cancer onset and progression.[247-249] In a randomized placebo-controlled trial involving 98 breast cancer patients taking tamoxifen, 150 mg of DIM twice daily for 12 months promoted favorable changes in estrogen metabolism. However, DIM also decreased the amount of tamoxifen-related compounds in circulation compared with placebo, suggesting it could reduce tamoxifen's effectiveness.[250] **Until more is known about this interaction, DIM should not be used by breast cancer patients taking tamoxifen.**

Flaxseeds

Reported dosage: 25 grams–50 grams daily

Flaxseeds have been studied for their potential role in breast cancer prevention and treatment mainly because of their high lignan content. Lignans are plant fibers that are digested by intestinal bacteria into phytoestrogens—compounds that alter estrogen signaling by binding ERs, blocking estrogen, and exerting weak estrogen-like activity. In addition, phytoestrogens from flaxseeds have antioxidant properties. Flaxseeds are also a rich source of alpha-linolenic acid, an omega-3 fatty acid, which has demonstrated anti-cancer effects in the laboratory and may lower breast cancer risk.[251]

Higher flaxseed and lignan intakes have been associated with lower breast cancer risk in multiple observational studies. The amount associated with this benefit is 30 grams (about one ounce) per day.[251] In a randomized controlled trial, 32 newly diagnosed postmenopausal breast cancer patients were given muffins with either 25 grams (about 2 tablespoons) of flaxseed with 50 mg of lignan or no flaxseed (placebo) to be eaten daily until surgery (an average of 32–39 days). Tumor cell proliferation and a breast tumor cell biomarker, c-erbB2, decreased significantly in the flax muffin group, while programmed tumor cell death increased. None of these changes were seen in the placebo group.[252] A trial lacking a control group investigated the effects of 50 mg of flaxseed lignan per day for 12 months in 45 premenopausal women with a high breast cancer risk. The participants had high Ki-67 expression levels in biopsy samples and either a history of prior breast cancer or precancerous breast changes. Lignan supplementation led to a reduction in Ki-67 in 36 (80%) participants and the percentage of women with precancerous cellular changes decreased.[253]

In one animal study, flaxseed consumption enhanced the anti-tumor effect of tamoxifen.[251] However, it is still not known whether flaxseed use can improve breast cancer survival outcomes.

Soy

Reported dosage: Approximately 60 mg of soy isoflavones or 2–3 servings of soy food daily

Dietary intake of soy-containing foods may improve outcomes in breast cancer.[147,254] Soybeans are an important source of phytoestrogens called isoflavones. Phytoestrogens, including soy isoflavones, have a structure that

allows them to bind to ERs and mildly stimulate estrogenic signaling. This leads to downregulation of estrogen signaling in conditions of high estrogen levels (such as pre-menstrually) or upregulation in conditions of low estrogen levels (such as after menopause).[255]

Isoflavones bind more strongly to ER-beta than ER-alpha. ER-alpha is the main ER type in breast and uterine tissue and contributes to estrogen-related cell proliferation.[256] Soy isoflavones also have epigenetic effects leading to reduced ER-alpha expression, making them potentially protective against breast cancer.[257] Finally, isoflavones have demonstrated a range of health benefits that may be related to their ability to reduce oxidative stress and inflammation and promote healthy metabolism.[258]

A recent systematic review and meta-analysis that included 11 observational studies evaluating the impacts of soy intake on breast cancer outcomes found greater intake of soy isoflavones (a type of phytoestrogen) was associated with a 26% reduced risk of breast cancer recurrence. Subgroup analysis showed high soy isoflavone intake was associated with a 28% lower recurrence risk in postmenopausal women and an 18% lower recurrence risk among patients with ER-positive cancer. A soy isoflavone intake of 60 mg per day, equivalent to about 2–3 servings of soy food (eg, soy milk, tofu, or cooked soybeans) per day, was linked to the greatest risk reduction. In addition, the analysis found higher soy protein or product intake was associated with a 25% reduction in cancer-related mortality in those with ER-positive breast cancer.[254]

Historical Concerns: Soy Phytoestrogens & Breast Cancer

Although concerns have historically been expressed about the potential for soy isoflavones (a type of phytoestrogen) to stimulate breast cancer cells, findings from observational studies suggest eating soy foods after a breast cancer diagnosis is safe and possibly beneficial.[259] Higher intake of soy and its isoflavones after a breast cancer diagnosis has been associated with lower recurrence risk and possibly longer overall survival.[260-262] In addition, observational evidence suggests eating soy foods does not interfere with endocrine therapy with tamoxifen or aromatase inhibitors. As a result, various cancer organizations around the world, including the American Cancer Society and the American Institute for Cancer Research, have issued position statements recognizing soy intake as safe and possibly helpful for breast cancer patients.[259]

Boswellia

Reported dosage: 2,400 mg daily; 2% Boswellia cream topically twice daily during radiation therapy

Boswellia (frankincense, *Boswellia serrata*) and its active compounds, boswellic acids, have demonstrated anti-cancer effects in a variety of cancer cell types and animal models. Boswellia has well-known anti-inflammatory activity and is widely used to treat such conditions as arthritis and asthma. In a small pilot trial, 18 breast cancer patients were treated with 2,400 mg of boswellia extract per day for a median of 11 days between diagnosis and surgery. Surgical specimens showed levels of Ki-67, a marker of tumor cell proliferation, were reduced by an average of 13.8% compared with biopsy samples. Similar assessments in 18 matched patients who did not receive boswellia showed Ki-67 levels increased by an average of 54.6% between biopsy and surgery.[263] In a randomized controlled trial,114 women undergoing radiation treatment for breast cancer received either a topical 2% boswellia cream or a placebo cream to use twice daily on irradiated skin throughout radiation therapy (generally five sessions per week for five weeks). The boswellia cream reduced the severity of acute radiation-related skin damage (assessed as redness) compared with a placebo cream: 49% of those treated with placebo and 22% of those treated with boswellia had the highest intensity of redness following radiation.[264]

Crocin

Reported dosage: 30 mg daily

Crocin is a carotenoid and the main active compound found in the yellow spice saffron (*Crocus sativus*). Like other carotenoids, crocin has anti-inflammatory and antioxidant properties.[265] Saffron and its carotenoids have demonstrated neuroprotective effects and have shown promise in the treatment of neurological disorders, including depression and anxiety.[266] In pre-clinical experiments, it has also demonstrated a number of anti-cancer properties.[265]

In a randomized controlled trial, 72 patients with non-metastatic HER2-positive or triple-negative breast cancer

were given either 30 mg of crocin or placebo daily during doxorubicin-based chemotherapy. At the end of treatment, depression and anxiety scores dropped by approximately 30–40% in the crocin group but had increased by approximately 30% in the placebo group. The crocin group also had longer survival, but this effect may have been due to chance as the study was small.[267] Longer and larger trials are needed to determine whether crocin can be beneficial as part of breast cancer treatment.

6 Repurposed Drugs in Breast Cancer

Metformin

Metformin is used to treat type 2 diabetes, though ongoing research has provided some preliminary evidence that it may provide some clinical benefit in certain types of breast cancer when combined with standard therapies.[268] Analysis of gene expression profiles in postmenopausal breast cancer survivors showed that metformin treatment induced gene expression patterns that might be protective against new tumor development.[269] Preclinical research suggests metformin can directly impair the growth and spread of breast tumors, as well as sensitize breast cancer stem cells to chemotherapy drugs.[270] However, various pharmacokinetic characteristics of metformin present a challenge for its use in cancer, and metformin's preclinically demonstrated anti-cancer effects require concentrations of the drug that are much higher than those achieved in treating type 2 diabetes.[271] Nevertheless, clinical data on the benefits of metformin for breast cancer patients are mixed, and benefits may be restricted to patients with specific disease characteristics or genomic profiles.[271,272]

Intriguingly, one study that examined data from 44,541 women who were monitored for approximately eight to 14 years found those with type 2 diabetes treated with metformin had a 14% lower incidence of estrogen receptor-positive breast cancer than those without type 2 diabetes, and the risk decreased with longer use of metformin. However, they also had a 25% higher incidence of estrogen receptor-negative and 74% higher incidence of triple-negative breast cancer than those who did not have diabetes.[273] Having diabetes worsens survival outcomes in women with hormone receptor-positive breast cancer, but treatment with metformin appears to reverse the negative impact of diabetes on disease-free survival, distant disease-free survival, and overall survival.[271,274,275]

Clinical trials have found metformin is not beneficial in breast cancer patients without diabetes. A large randomized controlled trial that included 3,649 women with high-risk non-metastatic breast cancer and without diabetes compared metformin to placebo after standard anti-cancer treatment, monitoring participants for up to 10 years. The trial found metformin was no better than placebo at improving survival, and this lack of effect was observed in women with both HR-positive and HR-negative cancers.[276] A meta-analysis of five smaller randomized controlled trials that included a combined total of 396 non-diabetic breast cancer patients found adding metformin to standard anti-cancer treatment did not slow progression or improve overall survival.[277] Another meta-analysis that included data from five randomized controlled trials with a total of 412 participants found metformin also had no effect on outcomes in non-diabetic women with metastatic or recurrent breast cancer.[278]

Statins

There is some limited evidence that statins (a family of drugs used to reduce high cholesterol levels) may improve mortality outcomes in breast cancer patients.[279] Large meta-analyses of observational data involving women with breast cancer have found statin use to be associated with a 25–27% lower risk of breast cancer recurrence, as well as an 18–20% lower risk of breast cancer-specific and 18% lower risk of all-cause mortality.[279-281] Although statins do not appear to reduce the risk of developing breast cancer, the associations between statins and breast cancer outcomes appear to be independent of timing of initiation of statin use (before or after breast cancer diagnosis) and choice of statin drug.[280] Another meta-analysis found statin use after breast cancer diagnosis was only linked to better cancer-specific survival in those with HR-positive tumors.[282] In addition, there is some limited evidence that combining statin use with cancer therapies may extend disease-free survival in triple-negative breast cancer patients.[283] One large observational study in Finland found statin use after breast cancer diagnosis reduced the relative risk of breast cancer death by 51% in those whose cholesterol levels decreased with statin therapy, but was unchanged in those whose cholesterol levels did not decrease.[284]

Statins may also play a role in reducing adverse side effects of cancer treatment. In a randomized placebo-controlled trial that included 89 women recently diagnosed with breast cancer, rosuvastatin (Crestor), taken during

and after chemotherapy for a total of six months, protected against chemotherapy-induced cardiotoxic effects linked to heart failure.[285] Observational studies comparing data from women with breast cancer who were taking statin drugs before and during chemotherapy with data from similar women who did not take statins found statin users had a lower risk of cardiotoxicity related to chemotherapy.[286,287] One interesting study compared the use of a 1% atorvastatin (Lipitor) gel on irradiated skin twice daily for six weeks to a placebo gel in 70 breast cancer patients receiving radiation therapy. Those who used topical atorvastatin had decreased severity of radiation-induced skin symptoms, including itching, pain, and edema.[288]

7 Support and Resources for Patients and Caregivers

If you have any questions on the scientific content of this protocol, please call a Life Extension Oncology Wellness Specialist at 1-866-864-3027.

Navigating the Healthcare System

Understanding insurance and financial assistance

For many people with breast cancer, diagnosis and treatment bring the burden of financial stress to an emotionally challenging time. Dubbed "financial toxicity," this type of stress is a well-known side effect of cancer care that may persist for years after diagnosis and has been shown to reduce quality of life, lead to treatment disruptions, and contribute to mortality.[289,290] It is critical for patients to work with their healthcare providers and insurance companies to make sure they understand the direct and indirect out-of-pocket costs of treatment and know how to access available resources. Measuring and monitoring the financial burden of treatment allows patients and their care team to consider adjustments to protocols that prioritize overall well-being.[290]

The **American Cancer Society** offers guidance for cancer patients seeking assistance with treatment expenses, as well as costs of day-to-day life while dealing with cancer.

Finding the right healthcare team

After receiving a breast cancer diagnosis, it is important to find a care team that can provide the best care possible while addressing the patient's unique condition, needs, and preferences.[291] In addition to one's primary care physician and other personal connections, there are numerous resources available for finding cancer care centers. For example, the **National Cancer Institute-designated cancer centers** are recognized for their rigorous standards, state-of-the-art research, and commitment to developing new and better approaches to preventing, diagnosing, and treating cancer.[292] The **Association of Community Cancer Centers** and the **Association of American Cancer Institutes** are other resources that provide profiles of member cancer centers by state. Important considerations for finding the right team and center are their location, facilities, specialties, and availability of multidisciplinary teams, as well as access to clinical trials. The **American Cancer Society** has a worksheet that can help a patient decide whether a particular doctor or center is a good fit for them.[291]

Finding a patient advocate

Partnering with a knowledgeable patient advocate can be very helpful in ensuring your interests are guiding decisions in your cancer care journey. There are several patient advocacy resources available to patients. Often, the treatment center at which you are receiving treatment will have patient advocacy resources available. Also, the American Cancer Society can provide access to patient navigators to assist patients. They can be reached at 1-800-227-2345. Local or statewide services may be available as well. For example, the **Patient Advocate Foundation** assists breast cancer patients in partnership with relevant local organizations. Insurance providers may provide specific resources related to patient advocacy and care navigation as well. Private patient advocacy services are available as well and may be worth pursuing for patients with disposable resources.

Update History

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The protocols raise many issues that are subject to change as new data emerge. None of our suggested protocol regimens can guarantee health benefits. Life Extension has not performed independent verification of the data contained in the referenced materials, and expressly disclaims responsibility for any error in the literature.

References

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†Ratings based on results of the 2025 ConsumerLab.com Survey of Supplement Users. Multivitamin rating based on results of the 2024 ConsumerLab.com Survey of Supplement Users. For more information, visit **www.consumerlab.com/survey**.

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