

# Breast Cancer and Lymphedema: A Narrative Review

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## Abstract

Breast cancer is the second most common cancer diagnosed worldwide, and the leading cause of cancer death in women. The understanding of disease presentation by patients and health care providers is crucial for a correct diagnosis and management. Preventive measures emphasize risk-reducing behaviors such as a healthy diet, reduced alcohol consumption, increased physical activity, and breastfeeding children. Screening techniques such as mammography, ultrasound, and MRI aid in early detection. Following the screening, a breast biopsy is performed, and a histopathological assessment is carried out to confirm a breast cancer diagnosis. In addition to surgery, radiotherapy, and lifestyle modifications, treatment regimens include a range of medications such as anti-hormonal drugs and chemotherapy. Lymphedema is a severe and major long-term consequence of breast cancer treatment. The major contributors to the diminished lymph drainage are a lumpectomy/mastectomy procedure that involves the surgical removal of lymph nodes, and radiotherapy. The fluid accumulation of lymphedema poses physical limitations to the patient and impacts the overall quality of life. A sentinel lymph node biopsy is an essential method of identifying the first draining lymph nodes affected by metastasis. This procedure allows surgeons to later remove only affected lymph nodes, sparing those that are unaffected and hence reduce the risk and magnitude of lymphedema development. Patients who receive education about lymphedema demonstrate higher compliance with treatment and self-care management practices. The purpose of this review is to provide information about breast cancer, the development of lymphedema, and how to recognize and manage both.

**Key Words:** Breast cancer; Lymphedema; Breast tumor; Review; Review literature (Source: MeSH-NLM).

## Introduction

Cancer is a disease process characterized by abnormal cell growth that can affect any part of the body. Benign tumors are confined to one part of the body, whilst malignant tumors spread via the blood or lymphatics to other parts of the body.<sup>1</sup> Amongst all cancer types, the most common is breast cancer (24.2%), followed by colorectal (9.5%), and lung cancer (8.4%). Of a total 4.2 million cancer deaths, breast cancer is the leading cause of cancer deaths in women (15%), followed by lung cancer (13.8%) and then colorectal cancer (9.5%).<sup>2</sup>

The mechanism of cancer development varies according to cancer type and origin, and the characteristics of the affected individual. Breast cancer development is mostly influenced by the presence of estrogen and progesterone hormones in the circulation giving rise to hormone receptor-positive breast cancer.<sup>3</sup> Less commonly, hormone receptor-negative cancer may arise. Other mechanisms include mutations in tumor suppressor genes, some of which are hereditary such as BRCA1 and BRCA2.<sup>4</sup>

Its widespread burden emphasizes the importance of screening, correct diagnosis, and treatment. The history and physical examination of the patient are important in the initial identification of suspected pathologies.<sup>4</sup> Imaging techniques such as mammography, ultrasound, MRI and CT have a role in further investigation of any abnormal findings.<sup>5</sup> The pathological findings detected through imaging are taken a final step further with a breast tissue biopsy providing the final diagnosis.<sup>6</sup>

Breast cancer is categorized according to 3 major classification systems: the histopathology of biopsied specimens, grade, or stage.<sup>7</sup> Each system establishes a final level of cancer spread and severity that determines the treatment regimen and predicted prognosis. Further to classification, presenting symptoms are organized into clusters, with

clusters of increased symptom number and severity foreshadowing a worse prognosis.<sup>8</sup> According to the incidence rates of organs typically affected, the metastasis of breast cancer affects lymph nodes (64%), lungs (57%), red bone marrow (55%), liver (51%), bone (49%), adrenals (34%), and the brain (10%).<sup>9</sup> Over 90% of women who develop breast cancer, have what is referred to as 'early breast cancer' in which cancer is confined to the breast and axillary lymph nodes.<sup>10</sup> Since the lymph nodes are the primary site of cancer spread, the impact of lymph node removal is an appropriate point of further discussion.

As part of the treatment process, affected lymph nodes (and sometimes unaffected lymph nodes) are removed during lumpectomy/mastectomy surgeries.<sup>11</sup> Due to the reduced capacity of the remaining lymph nodes to remove excess interstitial fluid, lymphedema develops as a consequence and affects between 12-28% of women treated for breast cancer.<sup>12</sup> Lymphedema may also occur after radiotherapy due to the formation of scar tissue impeding lymph flow. Lymphedema presents as swelling of the affected arm that involves pain, heaviness and a disrupted functioning of everyday tasks.<sup>11</sup> It may progress to a more severe fibrotic process and soft tissue destruction that manifest as warts, tissue bulges and open wounds.<sup>13</sup>

The management of lymphedema includes a range of compression therapies and physical therapy.<sup>14</sup> Because a large portion of treatment involves self-care practices, it is crucial that the patient is adherent, and has access to information regarding the therapeutic process and progress.<sup>15</sup>

Since breast cancer is a significant contributor to the overall burden of cancer, and its treatment is a recognized contributor to lymphedema, the link between breast cancer treatment and lymphedema is proven to be a valuable topic for research. The purpose of this literature review is to provide a basic understanding of the principles of breast cancer and lymphedema to patients, medical professionals, and the general public.

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Editors: Lukas Käsmann, Mihnea-Alexandru Găman

Student Editor: Nicholas Hui

Submission: Mar 2, 2019. Revisions: Mar 24, 2019; Oct 15, 2019; Oct 25, 2019

Acceptance: Nov 14, 2019. Publication: Dec 17, 2019

Process: Peer-reviewed

Papers were extracted from the PubMed database using varying combinations of the search terms breast cancer or breast carcinoma; presentation; diagnosis; classification; pathogenesis; management; and prevention. A second search that focused on the development of lymphedema included combinations of the search terms lymphedema; consequence; breast cancer; surgery; radiotherapy; diagnosis; classification; pathogenesis; management; and prevention. Papers were limited to human subjects, and the English language. Small-scale studies that were inconclusive or had results of no statistical significance were excluded. The literature was screened for the information considered to be most up-to-date and relevant to medical professionals and the wider public. The information was then extracted and summarized to be used for this review.

## Presentation

With the development of screening techniques such as mammography and other imaging modalities, breast cancer is usually detected prior to the development of obvious signs and symptoms. However, the signs and symptoms that may become apparent to the patient still pose as an important area of discussion. A first sign of breast cancer that is usually noticed by the patient is a lump in the breast that feels different to the surrounding tissue.<sup>16</sup> A change in shape, size and general breast appearance may be noted.<sup>1</sup> Further skin changes reveal skin erythema, peeling, scaling, and a characteristic dimpling resembling that of an orange peel known as *peau d'orange*.<sup>1</sup>

Nipple changes are often unilateral and include distortion, inversion, retraction or elevation, and eczematous skin changes from the nipple and surrounding areola that is unresponsive to topical treatment.<sup>1</sup> The nipple may also secrete a serous or bloody discharge.<sup>17</sup> If the cancer has spread to the lymph nodes, pain and swelling around the clavicles and axilla may be present.<sup>1</sup>

Symptoms often present concurrently in breast cancer patients.<sup>8</sup> The total burden of symptoms shows a negative correlation with the quality of life, with every additional symptom relating to a further decline.<sup>8</sup> Symptoms include physiological disturbances as well as psychological effects. The physiological aspect includes pain, numbness, disturbed sleep, decreased sex drive, weight changes, peripheral neuropathy, gastrointestinal disturbance, and spontaneous menopause.<sup>8-9</sup> The psychological symptoms include fatigue, anxiety, depression, perceived cognitive impairment, mood changes, and a lowered self-esteem.<sup>9</sup>

## Diagnosis

### Patient history and physical examination

The patient's history and physical examination establish the link between risk factors and symptomatology. Clinical history assesses the risk of cancer and includes questions regarding the age of menarche, pregnancies to date, menopausal status, and medications such as oral contraceptive and hormone replacement therapy. A family history of breast and ovarian cancer in first degree relatives should also be established.<sup>18</sup>

As part of the physical examination, the patient is first positioned sitting upright with the upper body exposed so that a thorough inspection can be carried out to identify breast asymmetry, nipple changes and discharge, and visible masses. Specific skin changes to look out for include skin erythema, dimpling, and *peau d'orange*. Palpation of the breast parenchyma then proceeds with the patient in the supine position and ipsilateral arm placed over the head. Cervical, supraclavicular and axillary lymph nodes are also palpated for signs of lymphadenopathy.<sup>18</sup>

### Imaging techniques

To further investigate suspicions of breast cancer, a range of imaging techniques are utilized. The American Cancer Society (ACS) recommends mammography as the primary mass screening technique for females between the ages of 40 and 74. However, the ionizing

radiation poses a limitation to its widespread use especially in pregnant females in which mammography is contraindicated. False-positive and false-negative results also limit mammography as a diagnostic tool in patients.<sup>5</sup> Mammography has a false-negative result of about 13%. The chance of having a false-positive result ranges from 7-12%, with younger women and women with dense breasts being more likely to have a false-positive result.<sup>5</sup>

Breast ultrasound (US) is used as a supplement to mammography to improve sensitivity. In using acoustic waves to reflect breast structures, cysts and solid masses can be identified.<sup>19</sup> However, healthy and cancerous tissue may present similar acoustic properties that ultrasound may fail to differentiate between.<sup>5</sup>

Magnetic resonance imaging (MRI) is non-invasive and non-ionizing, making it ideal for high risk patients who cannot undergo other screening and diagnostic procedures. Magnetic fields with radio frequency signals are applied to create cross-sectional images for the identification of tumor masses.<sup>17</sup> High costs, lack of availability, time consumption, and its high false-positive rate limit the widespread use of MRI.<sup>5</sup> It is also difficult to detect some types of cancers such as invasive ductal and lobular carcinoma using MRI, but it has a role in the identification of distant metastasis.

Computer tomography (CT) uses radioactive waves to provide cross-sectional images from different angles of the body. It provides images of soft tissue, bone, and blood vessels, making it useful for determining distant metastasis. However, CT has a low sensitivity and poses a radiation risk.<sup>5</sup> Position emission tomography (PET) involves the administration of a radioactive isotope and the detection of photons produced during the process of radioactive decay that interact with surrounding tissue.<sup>20</sup> PET is used for imaging distant metastasis and response to therapy. The use of ionizing radiation as well as a radioactive tracer limit its widespread use.<sup>5</sup>

### Breast biopsy and fine needle aspiration

After relevant imaging of the patient's breast, the final diagnosis is made based on the results of a biopsy. This involves removing cells from the breast tissue to be examined in a laboratory in order to identify abnormalities.<sup>6</sup> The literature describes surgical biopsy as the gold standard for breast diagnosis before the 1990's.<sup>6</sup> This subjected the patient to a cumbersome process and an invasive surgery which proved to be unnecessary in some cases.

As an advancement, percutaneous needle biopsy (PNB) emerged as the preferred method of breast diagnosis. Fine needle aspiration biopsy (FNAB) was the first to emerge in this category.<sup>6</sup> Following FNAB, the introduction of the image directed core needle biopsy revolutionized the field with its ability to obtain histological samples that provide diagnostic information not achieved by FNAB. It can distinguish invasive from non-invasive cancer, determine tumor grade, and expression of hormone receptors.<sup>6</sup>

The full extent of the disease can be assessed before surgery by sampling areas susceptible to cancer spread. The surgeon may request that a sentinel lymph node biopsy (SLNB) be performed to investigate the extent of metastasis to nearby lymph nodes.<sup>6</sup> A radioactive substance or a dye are injected near the tumor. The first few lymph nodes that drain the breast tissue will absorb the radioactive substance and be detected by a probe. These lymph nodes can then be removed and checked for cancerous cells.<sup>21</sup> Further to this, a decision can be made regarding the extent of lymph node removal based on whether cancerous cells are present or not.

## Classification

Tumors are mostly classified according to the histopathological features of biopsied specimens that are viewed under light microscopy.<sup>7</sup> Looking at the growth patterns and cytological features, two main categories of

breast cancer have been described: carcinoma in situ; and invasive (infiltrating) carcinoma. Breast carcinoma in situ is further classified as either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).<sup>22</sup> DCIS is the more common subtype and is sub-classified even further into five distinct types based on architectural features: comedo; cribriform; micropapillary; papillary; and solid. Invasive (infiltrating) carcinoma is further classified as: tubular; ductal lobular; invasive lobular; infiltrating ductal; mucinous (colloid); medullary; and infiltrating ductal.<sup>22</sup>

Another system classifies cancer according to grade and focuses on the appearance of cancer cells compared to normal tissue. The Scarff-Bloom-Richardson grading system allocates scores to features of breast tissue that include tubule formation, nuclear polymorphism, and mitotic count. The overall score classifies the tumor as grade 1 (well-differentiated, good prognosis), grade 2 (moderately differentiated, medium prognosis), or grade 3 (poorly differentiated, worse prognosis).<sup>23</sup>

The third system classifies cancer according to the stage, and follows the TNM (tumor, lymph node involvement, and metastasis) system. This system describes the severity of cancer and assists with the selection of appropriate treatment in conjunction with other factors such as the presence of estrogen and progesterone receptors.<sup>24</sup>

The Breast Imaging Report and Data System (BI-RADS) is a communication tool described by the American College of Radiology (ACR) to reduce variability when creating mammography, ultrasound, and MRI reports. It uses a standardized approach to define the features of a breast mass by detailing the density, location, micro/macrocalfications, architectural distortions, and associated findings.<sup>25</sup> By doing this, BI-RADS aids in the reproducibility and comparison of radiological descriptions of breast cancer findings. **Table 1** describes the BI-RADS classification in more detail.

**Pathogenesis**

The pathogenesis of breast cancer is variable across populations as it depends on an interaction between environment, lifestyle, and genetic susceptibility.<sup>18</sup> Several mechanisms contribute to the unchecked proliferation of breast tissue.

**Hormone receptor-positive breast cancer (ER+ and PR+)**

Estrogen and progesterone are central in regulating the growth and differentiation of mammary glands.<sup>3</sup> The effects of estrogen are mediated through its binding to estrogen receptors ER-a and ER-b, and those of progesterone to the progesterone receptor (PR).<sup>3</sup> Although the exact mechanism is not understood, the binding of estrogen and progesterone to their respective receptors on cancerous cells, leads to altered gene activity and uncontrolled ER- or PR-mediated breast tissue proliferation.<sup>26</sup> Approximately 80% of all cancers are ER-positive, and 65% of these are also PR-positive. The age-specific statistics suggest that there is an increased incidence rate of breast cancer before menopause (ages 40-50) that tends to slow down after this probably due to the decreased levels of circulating estrogens produced by the ovaries.<sup>27</sup> However, sources of these hormones are also exogenous in the form of the oral contraceptive pill (in pre-menopausal women) or hormone replacement therapy (in post-menopausal women).<sup>26</sup> An increased risk of breast cancer has been established in women who take these medications.<sup>26-28</sup>

**HER-2 overexpression**

HER-2 (human epidermal growth factor 2), otherwise known as ERBB2 (Erb-B2 receptor tyrosine kinase 2) is a receptor tyrosine protein kinase found on breast cells that accounts for 25-30% of breast cancers when overexpressed.<sup>29</sup> Under normal conditions, this receptor is found on breast cells to stimulate breast development.<sup>29</sup>

**Table 1.** BI-RADS Classification.<sup>25</sup>

Category	Explanation	Chance of malignancy	Action
0	Incomplete evaluation	N/A	Further imaging required
1	Negative examination. No masses, suspicious calcifications, or areas of architectural distortion	0%	Normal interval follow-up
2	Benign. Secretory calcifications, simple cysts, fat containing lesions, calcified fibroadenomas, implants, and intramammary lymph nodes	0%	Normal interval follow-up
3	Probably benign. Non-palpable circumscribed mass on baseline mammogram, a focal asymmetry, or a solitary group of punctate calcifications	<2%	Shortened interval follow-up
4	Suspicious findings	A - 2-10% B - 10-50% C - 50-95%	Biopsy considered
5	Highly suggestive of malignancy	>95%	Biopsy or surgery
6	Proven malignancy	N/A	Imaging for cancer staging or evaluation after chemotherapy

*Legend:* Derived from 'BIRADS classification in mammography' *European Journal of Radiology* 61(2007) pp. 192-194.<sup>25</sup>

**Tumor suppressor gene mutations**

The PI3K/AKT pathway is important in regulating the cell cycle by initiating downstream survival signals that protect the cell from premature death.<sup>30</sup> This pathway is regulated by the tumor suppressor protein, PTEN, that turns off the PI3K/AKT by initiating apoptosis when conditions are appropriate.<sup>31</sup> Mutations in PTEN lead to a constantly activated PI3K/AKT pathway that in effect causes inappropriate proliferation.<sup>31</sup>

Five percent of breast cancer cases are attributed to genetic mutations in the tumor suppressor genes BRCA1 and BRCA2.<sup>18-32</sup> Of the hundreds of mutations identified, some have no impact, while others are involved in the development of hereditary breast-ovarian cancer syndrome that is responsible for breast and ovarian cancer in genetically related families.<sup>33</sup>

**Management**

The management and treatment of breast cancer vary according to disease type and severity, age, the overall health of the patient, and personal treatment preference.<sup>34</sup> In the early stages, local therapy such as surgery and radiotherapy are effective, whereas in advanced and metastatic cases, systemic therapy is preferred.<sup>35</sup> Compared to age-matched women without the disease, the 5-year survival of women with breast cancer has increased from 80% in the 1950's to 89% today.<sup>11</sup>

### Surgery & Radiation Therapy

The initial management of breast cancer is surgery.<sup>34</sup> A more conservative lumpectomy (solitary lump removal), is the preferred surgical therapy when the tumor is smaller than 4cm in size.<sup>36</sup> A mastectomy (complete breast resection) is the treatment of choice when the patient presents with tumors in different breast areas, tumors that are large in relation to the breast, instances where radiotherapy is inaccessible to the patient, or when the patient requests to avoid systemic therapy.<sup>36</sup>

During the mastectomy surgery, axillary lymph nodes may also be removed to determine the extent of metastasis. These changes affect the lymph drainage of the ipsilateral arm, leading to lymphedema.<sup>11</sup>

Radiation therapy serves as an adjunct to lumpectomy and mastectomy surgeries, as a means of reducing local cancer recurrence.<sup>35</sup> Radiation therapy uses high energy X-rays or gamma rays to eradicate cancerous cells that either recur after tumor removal, or remain after surgery.<sup>37</sup> External beam radiation is the most common type of radiotherapy that utilizes energy from a machine exterior to the body.<sup>37</sup>

Due to the high intensity of the radiation, normal tissue surrounding cancerous tissue is also damaged. However, healthy tissue has a repair response that cancer cells lack, so radiation therapy is given over an extended period of 5-7 weeks to allow for recovery of the normal tissue.<sup>35</sup> Patients may experience fatigue, muscle stiffness, swelling, or tenderness during the treatment period as well as a change in skin color resembling that of a sunburn.<sup>37</sup> Similar to mammography, due to the high energy radiation, this therapy is contraindicated in pregnant patients.<sup>35</sup>

### Development of Lymphedema

Under normal conditions, the role of the lymphatic system is to maintain fluid balance in tissues, fight infection and remove cellular debris from extracellular spaces. The venules reabsorb 90% of fluids that are filtered from the capillaries into the *interstitium* - the remaining 10% of fluid and proteins are removed by the lymphatic vessels to be returned to the bloodstream.<sup>11</sup> The lymphatic system thus balances the inward and outward flow, creating a stable overall interstitial pressure. A disruption of this balance results in lymphedema - an abnormal accumulation of interstitial fluid that leads to chronic inflammation and possible fibrosis.<sup>38</sup>

Lymphedema in the context of breast cancer is secondary to therapeutic interventions such as the resection of axillary lymph nodes or radiation therapy.<sup>38</sup> Lymph node removal compromises the overall drainage capacity of the lymphatic system. Superficial scarring following surgery or scarring post-radiotherapy may impede the lymphatic flow across the scar tissue leading to fluid accumulation proximal to the scar.<sup>11</sup> Localized post-surgery infection also leads to an increased volume of fluid and cellular components that may exceed the transport capacity of the impaired lymphatic system.<sup>10</sup>

Areas commonly affected by the diminished lymph flow are those that generally drain to the axilla such as the ipsilateral breast, chest, upper trunk, arm, and hand.<sup>11</sup> Increased age (>60 years), obesity (BMI >25), and a more extensive axillary lymph node dissection are associated with an increased risk of post-operative lymphedema.<sup>38</sup>

Hayes et al., conducted a study in which 33% of women developed lymphedema 6-18 months after breast cancer surgery.<sup>39</sup> A greater odds were associated with older age, treatment complications, and more extensive surgery (axillary node dissection, mastectomy, greater number of lymph nodes removed).<sup>39</sup> The risk of developing lymphedema post-radiotherapy is directly related to the radiation dose. The combination of surgery and radiotherapy poses an even higher risk.<sup>38</sup> Having a partner and partaking in regular activity was associated with a lower odds of lymphedema development.<sup>39</sup>

The typical presentation of lymphedema after breast cancer is local swelling in one or both arms.<sup>13</sup> Typical symptoms accompanying this include pain, heaviness, limited range of motion, and disruption of daily function - in particular, tasks involving gross and fine motor skills.<sup>13</sup> Early signs include swelling that pits with applied pressure. As the disease progresses, patients may present with fibrosis and fat accumulation in the affected area. Warts, skin folds and papules may present at later stages.<sup>40</sup> The patient may complain of impaired mobility and notice physical changes such as clothing or jewelry being too tight, difficulty writing, arm/hand puffiness, indentations, firm or leathery skin, and swelling after exercise.<sup>39</sup>

Unlike breast cancer diagnosis, there is uncertainty around lymphedema diagnosis amongst physicians. However, diagnosis is commonly made upon a measurable 2cm (or more) difference in arm circumference or 200mL difference in limb volume between affected and non-affected limbs.<sup>11</sup> A range of diagnostic evaluations have been identified to confirm lymphedema. Soft tissue imaging such as MRI, computed tomography (CT), and ultrasound assist in the detection of excess interstitial fluid. Lymphoscintigraphy, a nuclear medicine technique that images lymph vessels and nodes, detects slow or absent lymph flow. Bio-impedance spectroscopy (BIS) measures water content in tissues and has been especially useful in diagnosing breast cancer related lymphedema.<sup>41</sup>

Lymphedema progression can be established by examining tissue changes that are categorized into three stages: Stage I is characterized by pitting upon application of pressure that subsides with limb elevation. Stage II is characterized by increased fibrosis and fat accumulation that no longer pits with applied pressure and does not subside with limb elevation. Stage III represents fibrotic progression that encompasses a range of soft tissue manifestations such as warts, skin folds and papules that lead to impaired mobility and infection susceptibility.<sup>40</sup>

Two principal methods for managing breast cancer-related lymphedema are described: complex decongestive therapy (CDT); and exercise.<sup>14</sup> CDT is divided into two parts: an intensive phase which consists of four components, and a maintenance phase in which the patient practices self-care with occasional manual lymph drainage (MLD) by a therapist.

The four parts of the intensive phase include MLD, arm and shoulder exercises, compression therapy, and deep-breathing practices that promote venous and lymphatic flow.<sup>14</sup> Exercise for patients with lymphedema follows supervised programs with goals to restore range of motion (ROM) and upper limb function, increase muscle strength, and to control swelling.<sup>14</sup> Reduction in weight also helps lessen lymphedema.<sup>42</sup>

Educating patients about secondary lymphedema, and subsequent management should not be underestimated. Many patients report not having received sufficient information about lymphedema as a complication of breast cancer.<sup>43</sup> The use of lymph drainage massage services and compression garments was found to be utilized more amongst women who had received lymphedema education.<sup>15</sup> A positive correlation between patient education and adherence to lymphedema therapy is demonstrated, emphasizing the importance of patient education.<sup>14</sup>

Lymphedema prevention can be divided into pre-surgery and post-surgery techniques. Already mentioned as part of diagnostic techniques, a sentinel lymph node biopsy is the most important method of identifying lymph node metastasis.<sup>44-45</sup> Through identifying the axillary lymph nodes most likely to be affected by tumor metastases, it is possible to avoid unnecessary nodal dissection and hence lymphedema as a consequence.<sup>45</sup> This benefit is proven in a meta-analysis showing the rate of lymphedema as a complication following axillary dissection is four times higher than following sentinel

node biopsy.<sup>46</sup> Further to this, chemotherapy shows a protective effect against lymphedema development: 20-40% of node-positive patients tested node-negative after chemotherapy, so a sentinel node biopsy performed after chemotherapy could reduce unnecessary axillary dissection.<sup>46</sup>

Due to the difficulty in predicting populations at risk for developing lymphedema after undergoing breast cancer surgery, clinicians recommend risk-reducing behavior as the primary preventative measure in all patients undergoing axilla surgery.<sup>47</sup> The most widely recognized of these is the avoidance of venipuncture, injections, or taking blood pressure on the side of the affected arm, as well as the use of compression sleeves for air travel.<sup>47</sup> Women who receive lymphedema education prior to treatment, exercise regularly, and implement preventative self-care activities demonstrate a lower incidence of lymphedema following breast cancer surgery.<sup>14, 48</sup>

### Systemic therapy

Systemic therapy treats cancer cells throughout the body using a range of medications and is subdivided into chemotherapy, endocrine (hormone) therapy, and targeted therapy.<sup>34-35</sup> The National Institute for Health Care Excellence (NICE) guidelines describe the populations in which chemotherapy is indicated. Adjuvant anthracycline-taxane combination chemotherapy is recommended in patients with invasive breast cancer who are at risk of disease recurrence. Neoadjuvant chemotherapy is offered to reduce the tumor size in patients with ER-invasive breast cancer and is considered in patients with ER+ invasive breast cancer. Neoadjuvant chemotherapy is given in combination with trastuzumab in patients with HER2+ invasive cancer.<sup>34</sup>

NICE recommend that docetaxel is given as single-agent first-line therapy; vinorelbine or capecitabine as single-agent second-line treatment; vinorelbine or capecitabine (whichever was not used as second-line treatment) as single-agent third line treatment.<sup>34</sup> Alternative options for second-line treatments are Everolimus and Fulvestrant, and a third line alternative is Eribulin.<sup>34</sup> Chemotherapy side effects include nausea and vomiting, hair loss, fatigue, mouth ulcers, dry and cracked skin, depression, weight changes, and an unpleasant taste in the mouth.

Endocrine therapy is indicated for patients with ER+ tumors, and is administered after surgery, radiotherapy, and chemotherapy with the purpose of preventing relapse.<sup>48</sup> Tamoxifen, which acts by inhibiting estrogen receptors, is the medication of choice for pre-menopausal women.<sup>34, 48</sup> Aromatase inhibitors (either steroidal or non-steroidal) that act by lowering the amount of circulating estrogen are indicated for post-menopausal women.<sup>34</sup> Patients who experience hot flushes as an adverse effect of hormone therapy, can reduce this by avoiding triggers such as caffeine, alcohol, and smoking. In cases where symptoms persist, serotonin-norepinephrine receptor inhibitors (SNRIs) such as venlafaxine may be administered.<sup>49</sup>

Trastuzumab (otherwise known as Herceptin) in combination with paclitaxel is the medication of choice for tumors that are hormone

receptor-negative and HER2-positive.<sup>34</sup> Trastuzumab is a monoclonal antibody that blocks HER2 protein activity in breast cancer cells and hence halts tumor growth.<sup>29</sup>

### Prevention

Since the leading risk factor for developing breast cancer stems from prolonged exposure to endogenous hormones, it is not easily modifiable.<sup>51</sup> Primary prevention of breast cancer is achieved by partaking in physical activity, maintaining a healthy weight, following a healthy diet, minimizing alcohol consumption, breastfeeding children, and minimizing the use of oral contraceptive pills and hormone replacement therapy.<sup>51</sup> Testing for BRCA1 and BRCA2 mutations is recommended in women with affected family members.<sup>52</sup> A bilateral mastectomy may be performed as prophylaxis for women who test positive for the mutations which are associated with increased risk of breast cancer.<sup>52</sup>

Estrogen receptor antagonists such as tamoxifen reduce the risk of breast cancer, but at the expense of an increased risk of endometrial cancer and thromboembolic events.<sup>53</sup> Because of this, they are reserved for treatment, and prevention only in high risk women.<sup>53</sup>

### Conclusion

It is evident from the literature that breast cancer is a prevalent disease that affects women on a worldwide scale. It is also thoroughly described that breast cancer presents itself through a range of physical symptoms and clinical findings. This emphasizes the importance of screening techniques that aid in the early detection of the disease, and preventive measures. The limitations posed by each imaging technique (mammography, ultrasound, and MRI) suggest that each patient needs to be considered on an individual basis to select the most suitable method per patient. Treating breast cancer follows a similar individualized method, considering the mechanism of cancer pathogenesis through assessing hormonal exposure and gene overexpression.

Because breast cancer is in most cases confined to the breast and axillary lymph nodes, the adverse effects that arise through lymph node resection are just as crucial as the adverse effects that arise through breast resection. Functional impairment, psychological distress, and disturbed daily routine are some of the significant effects of lymphedema that require management. The literature provides evidence that effective lymphedema management relies on the patient's will to comply with self-care practices. For this reason, patient education is crucial.

Continuous research and development are underway to develop highly specific treatment regimens that target breast cancer on a molecular genetic level. The advancement of the sentinel lymph node biopsy also has positive implications for reducing lymphedema as a complication of breast cancer metastasis and treatment. This suggests a promising overall prognosis for the general female population moving forward.

## References

- Watson M. Assessment of Suspected Cancer. *InnovAiT*. 2008 Feb;1(2):94-107.
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov;68(6):394-424.
- Gross JM, Yee D. How does the estrogen receptor work? *Breast Cancer Res*. 2002 Apr;4(2):62.
- Shah C, Arthur DW, Wazer D, Khan A, Ridner S, Vicini F. The impact of early detection and intervention of breast cancer-related lymphedema: a systematic review. *Cancer Med*. 2016 Jun;5:154-62.
- Wang L. Early Diagnosis of Breast Cancer. *Sensors*. 2017 Jul;17(7):1572.
- Calhoun KE, Anderson BO. Needle Biopsy for Breast Cancer Diagnosis: A Quality Metric for Breast Surgical Practice. *J Clin Oncol*. 2014 Jul;32(21):2191-2.
- Weigelt B, Horlings HM, Kreike B, Hayes MM, Hauptmann M, Wessels LFA, et al. Refinement of breast cancer classification by molecular characterization of histological special types. *J Pathol*. 2008 Oct;216(2):141-50.
- Marshall SA, Yang CC, Ping Q, Zhao M, Avis NE, Ip EH. Symptom clusters in women with breast cancer: an analysis of data from social media and a research study. *Qual Life Res*. 2016 Mar;25(3):547-57.
- Brem S, Kumar NB. Management of Treatment-Related Symptoms in Patients With Breast Cancer. *Clinical Journal of Oncology Nursing*. 2011 Feb;15(1):63-71.
- Zampell JC, Haimovitz-Friedman A, Mehrara BJ, Daluvoy SV, Avraham T, Cordeiro AP, et al. Radiation therapy causes loss of dermal lymphatic vessels and interferes with lymphatic function by TGF- $\beta$ 1-mediated tissue fibrosis. *Am J Physiol Physiol*. 2010 Sep;299(3):C589-C605.
- Wanchai A, Armer JM, Stewart BR, Lasinski BB. Breast cancer-related lymphedema: A literature review for clinical practice. *International Journal of Nursing Sciences*. 2016 Apr;3(2016):202-7.
- Basta MN, Fox JP, Kanchwala SK, Wu LC, Serletti JM, Kovach SJ, et al. Complicated breast cancer-related lymphedema: Evaluating health care resource utilization and associated costs of management. *Am J Surg*. 2016 Jan;211(1):133-41.
- Disipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol* 2013 May;14:500-15.
- Cheifetz O, Haley L. Management of secondary lymphedema related to breast cancer. Vol. 56, *Can Fam Physician*. 2010 Dec;56(12):1277-84.
- Bani HA, Fasching PA, Lux MM, Rauh C, Willner M, Eder I, et al. Lymphedema in breast cancer survivors: Assessment and information provision in a specialized breast unit. *Patient Educ Couns*. 2007 Jun;66(3):311-8.
- Provencher L, Hogue JC, Desbiens C, Poirier B, Poirier E, Boudreau D, et al. Is clinical breast examination important for breast cancer detection? *Curr Oncol*. 2016 Aug;23(4):332-9.
- Schneble EJ, Graham LJ, Shupe MP, Flynt FL, Banks KP, Kirkpatrick AD, et al. Future directions for the early detection of recurrent breast cancer. *J Cancer*. 2014 Mar;5(4):291-300.
- Shah R. Pathogenesis, prevention, diagnosis and treatment of breast cancer. *World J Clin Oncol*. 2014 Aug;5(3):283-298.
- Hooley RJ, Scoutt LM, Philpotts LE. Breast ultrasonography: State of the art. *Radiology* 2013;Sep 268(3):642-59.
- Pennant M, Takwoingi Y, Pennant L, Davenport C, Fry-Smith A, Einsinga, et al. A systematic review of positron emission tomography (PET) and positron emission tomography/computer tomography (PET/CT) for the diagnosis of breast cancer recurrence. *Health Technol Assess*. 2010 Oct;14(50):1-103.
- Yuan L, Qi X, Zhang Y, Yang X, Zhang F, Fan L, et al. Comparison of sentinel lymph node detection performances using blue dye in conjunction with indocyanine green or radioisotope in breast cancer patients: a prospective single-center randomized study. *Cancer Biol Med*. 2018 Nov;15(4):452-60.
- Malhotra GK, Zhao X, Band H, Band V. Histological, molecular and functional subtypes of breast cancers. *Cancer Biol Ther*. 2010 Nov;10(10):955-60.
- Howell LP, Gandour-Edwards R, O'Sullivan D. Application of the Scarff-Bloom-Richardson tumor grading system to fine-needle aspirates of the breast. *Am J Clin Pathol* 1994 Mar;101(3):262-5.
- Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017 Mar;67(4):290-303.
- Balleguier C, Ayadi S, Van Nguyen K, Vanel D, Dromain C, Sigal R. BIRADS classification in mammography. *Eur J Radiol*. 2007 Feb;61(2):192-4.
- Travis RC, Key TJ. Oestrogen exposure and breast cancer risk. *Breast cancer Res*. 2003 Jul;5(5):239-47.
- Henderson BE, Ross R, Bernstein L. Estrogens as a Cause of Human Cancer: The Richard and Hinda Rosenthal Foundation Award Lecture. *Cancer Res*. 1988 Jan;15:48(2):246-53.
- Cavaliere E, Chakravarti D, Guttenplan J, Hart E, Ingle J, Jankowiak R, et al. Catechol estrogen quinones as initiators of breast and other human cancers: Implications for biomarkers of susceptibility and cancer prevention. *Biochim Biophys Acta*. 2006 Aug;1766(1):63-78.
- Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *N Engl J Med*. 2001 Mar;344(11):783-92.
- Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR Signaling in Cancer. *Front Oncol*. 2014 Apr;4:64.
- Vara JÁF, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. PI3K/Akt signalling pathway and cancer. *Cancer Treat Rev* 2004 Apr;30(2):193-204.
- Dunning AM, Healey CS, Pharoah PDP, Teare MD, Ponder BAJ, Easton DF. A Systematic Review Of Genetic Polymorphisms and Breast Cancer Risk. *Cancer Epidemiol. Biomarkers Rev*. 1999 Oct;8(10):843-54.
- Moyer VA. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2014 Feb;160(4):271-81.
- NICE. Managing advanced breast cancer. *NICE Pathways* 2018 Jul;(2):1-22. Available from: <https://www.nice.org.uk/guidance/ng101/chapter/Recommendations#adjuvant-chemotherapy-for-invasive-breast-cancer>. Last accessed: Dec 17, 2019
- Brown LC, Mutter RW, Halyard MY. Benefits, risks, and safety of external beam radiation therapy for breast cancer. *Int J Womens Health* 2015 Apr;7:449-58.
- Livingston EH, Li HC. Breast Cancer Surgery: Less Is More. *JAMA* 2017 Sep 12;318(10):909-911.
- Breastcancer.org. Types of Radiation Therapy for Breast Cancer. 2018. Available from: <http://www.breastcancer.org/treatment/radiation/types>. Last accessed: Dec 17, 2019
- Sakorafas GH, Peros G, Cataliotti L, Vlastos G. Lymphedema following axillary lymph node dissection for breast cancer. *Surg Oncol* 2006 Nov;15(3):153-65.
- Hayes SC, Janda M, Cornish B, Battistutta D, Newman B. Lymphedema after breast cancer: Incidence, risk factors, and effect on upper body function. *J Clin Oncol* 2008 Jul;26(21):3536-42.
- International Society of Lymphology (ISL). The diagnosis and treatment of peripheral lymphedema: 2013 consensus document of the international society of lymphology. *Lymphology*. 2013 Mar;46(1):1-11.
- Cornish B, Chapman M, Hirst C, Mirolo B, Bunce LH, Ward L, et al. Early Diagnosis of Lymphedema Using Multiple Frequency Bioimpedance. *Lymphology*. 2001;34:2-11.
- Shaw C, Mortimer P, Judd PA. Randomized controlled trial comparing a low-fat diet with a weight-reduction diet in breast cancer-related lymphedema. *Cancer*. 2007 May;109(10):1949-56.
- Thomas-Maclean R, Miedema B, Tatemichi SR. Women's experiences with an underestimated condition. *Can Fam Physician*. 2005 Feb;51(2):246-247

44. Tripathi S, Trasil H, Telisinghe PU. Methylene blue for sentinel lymph node localisation in breast cancer surgery: Experience of RIPAS Hospital. *Brunei Int Med J.* 2010 Dec;6(3):117-21.
45. Cheng G, Kurita S, Torigian DA, Alavi A. Current status of sentinel lymph-node biopsy in patients with breast cancer. *Eur J Nucl Med Mol Imaging.* 2011 Mar;38(3):562-75.
46. Taghian AG, Brunelle CL, Sayegh HE, Gillespie TC, Daniell KM. Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. *Gland Surg.* 2018 Aug;7(4):379-403.
47. McLaughlin SA, Staley AC, Vicini F, Thiruchelvam P, Hutchison NA, Mendez J, et al. Considerations for Clinicians in the Diagnosis, Prevention, and Treatment of Breast Cancer-Related Lymphedema: Recommendations from a Multidisciplinary Expert ASBrS Panel. *Ann Surg Oncol.* 2017 Aug;24(10):2818-26.
48. Park JH, Lee WH, Chung HS. Incidence and risk factors of breast cancer lymphoedema.' *J Clin Nurs* 2007 Jun;(11):1450-9.
49. Kligman L, Younus J. Management of hot flashes in women with breast cancer. *Curr Oncol* 2010 Frb;17(1):81-6.
50. van Geel AN. Prophylactic mastectomy: The Rotterdam experience. *Breast.* 2003 Dec;12(6):357-61.
51. Hwang ES, Nho J. Lifestyle Intervention for Breast Cancer Women. *J Lifestyle Med.* 2019 Jan;9(1):12-14.
52. Hartmann LC, Schaid DJ, Woods JE, Crotty TB, Myers JL, Arnold P, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med.* 1999 Jan;340(2):77-84.
53. Nelson HD, Smith B, Griffin JC, Fu R. Use of Medications to Reduce Risk for Primary Breast Cancer: A Systematic Review for the US Preventive Services Task Force. *Ann Intern Med.* 2013 Apr;158(8):604-614.

#### Acknowledgments

None.

#### Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

#### Author Contributions

Conceptualization: AM, CC. Methodology: AM. Formal Analysis: AM, CC. Data Curation: AM. Investigation: AM. Writing – Original Draft: AM. Writing – Review & Editing: AM, CC. Visualization: AM.

#### Cite as:

Michaelides A, Constantinou C. Breast Cancer and Lymphedema: A Narrative Review. *Int J Med Students.* 2019 Sep-Dec;7(3):66-72.

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ISSN 2076-6327

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