INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy amongst women, breast cancer mortality worldwide is 25% greater than that of lung cancer in women and the second leading cause of cancer death in the united states ***(Abeloff et al., 2008).***

Both incidence and death rates for breast cancer have been declining in the last few years. Nevertheless, in 2005 by the Society for Women's Health Research indicated that breast cancer remains the most feared disease, even though heart disease is a much more common cause of death among women. Incidence of breast cancer in men are approximately 100 times less common than in women, but men with breast cancer are considered to have the same statistical survival rate as women ***(American Cancer Society, 2012)***.

Early detection & screening programs must be considered the best choice for reducing mortality from breast cancer ***(Letton et al., 2012).***

Early detection means using an approach that allows earlier diagnosis of breast cancer. Early detection improves the chances that breast cancer can be diagnosed at an early stage and treated successfully. Breast cancer that diagnosed during screening examinations is more likely to be small and still confined to the breast. In contrast, breast cancer that is detected because it is causing symptoms tends to be relatively larger and is more likely to have spread beyond the breast ***(Silverstien et al., 2012).***

Individuals with breast cancer have a 20-30% chance of having at least one relative with the disease. However, only 5-10% of the cases are a direct result of gene mutations in highly penetrable genes, such as BRCA1 and BRCA2 (BRCA1/2) as well as gene TP53 ***(Edlich et al., 2009).***

The function of these two genes is classified as tumour suppressors, is linked with key metabolic mechanisms such as DNA damage repair, regulation of gene expression and cell cycle control. The pathological BRCA allelic variants may cause alteration of protein function, transcriptional activity and DNA repair. Accumulation of the defects leads to widespread chromosome instability that may be directly responsible for cancer formation ***(Kurian et al., 2011).***

Owing to the significant breast cancer risk associated with BRCA1 or BRCA2 mutations, women with these mutations have several options available to them by which to reduce the risk of breast cancer. These include surgical (prophylactic mastectomy and prophylactic oophorectomy) and medical (chemoprevention) options. The breast cancer risk reductions associated with these options range from a 90% risk reduction associated with prophylactic mastectomy to approximately 50% with oophorectomy or tamoxifen. This is a major decision that requires time and a multidisciplinary approach ***(Metcalfe, 2009).***

Breast tissue can be sensitive to developing cancer. The female hormone estrogen stimulates breast cell division, which can increase the risk of breast cancer. Furthermore, breast cells are not fully mature in girls and young women who have not

had their first full-term pregnancy. Breast cells which are not fully mature bind carcinogens more strongly than and are not as efficient at repairing DNA damage as mature breast cells. Therefore, it's very important to reduce exposure to cancer causing agents during critical periods in a woman's life ***(Metcalfe, 2009).***

Besides host factors, the propensity of breast cancer to give rise to distant metastasis depends upon the molecular type of breast cancer. And the gene expression profile may predict the risk of distant recurrence. Breast cancers are often divided into four molecular subtypes based on their gene expression profiles (The luminal A, The luminal B, HER2-enriched, and Basal like). These subtypes have preferential sites for distant relapse. And the subtype may be also associated with efficacy of systemic cancer therapies ***(Greene, 2010).***

The gene- array based breast cancer molecular subtypes have been approximated using a panel of surrogate markers (estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor -2 (HER2), epidermal growth factor receptor (EGFR) and cytokines 5 (ck5)) as assisted by immunohistochemistry. Such immunohistochemistry-based have roughly similar characteristics and behavior as the respective subtypes defined by gene expression array. And they also predict for the site of distant metastasis ***(Smith et al., 2011).***

Not only histological type, grade, tumor size, Lymph node involvement (which were the only dependable factors in diagnosing and prognosing the tumor). But also Estrogen receptor (ER) and HER2 – receptor status all influence prognosis and probability of response to systemic therapies and the clinical course of breast cancer ***(Edlich et al., 2009).***

Today, there are many more options available for treating breast cancer. In recent years the number of effective treatments available has increased. Breast cancer has been treated with the standard therapies of radiotherapy, chemotherapy and surgery. These entire methods treat the cancer but affect healthy tissues as well as cancer tissues depends on specific molecules that influence growth and spread of cancer cells. But they are usually combined with chemotherapy to more effectively block growth of cancer cells. Targeted therapies do their work on specific cancer cells and not working on healthy tissues ***(Kurian et al., 2011).***

AIM OF THE WORK

The aim of the work is to provide an overview of the pathological types and biological nature of breast cancer in order to review the recent lines of the management of breast cancer according to biological classification.

ANATOMY OF THE BREAST

Embryological origin:

The epithelial lining of the ducts and acini of the breast is developed from ectoderm and the supporting tissue is derived from the mesenchyme. On each side of the ventral surface of young embryo, a thickened band of ectoderm develops (**the milk ridge**). 1t extends from the axilla to the inguinal region. In the human, the whole of this ridge atrophies, except only a small portion in each pectoral region from which the breast arises. Accessory breast tissue will form along the course of the milk ridge, if it does not disappear outside the area where the breast normally develops. Normally, a tiny portion of the ridge which is going to form the breast enlarges projecting slightly on the skin and extending deeply in the shape of buds which form long slender tubes from which the ducts and secreting tissue of the breast are formed. The nipple is either flat or depressed at birth, but later it projects beyond the surrounding skin ***(Ellis et al., 2003).***

Blood supply of the breast:

- **Arterial supply:**

Blood supply to the breast is from multiple sources:

1. **The internal mammary artery:** This arises from first part of subclavian artery, gives perforating branches (most notably the second to fifth perforators) supply the breast.
2. **The thoracoacromial artery:** it is a short branch of second part of the axillary artery.
3. **The lateral thoracic artery:** from second part of axillary artery
4. **The terminal branches of the third to eighth intercostal vessels and the vessels to serratus anterior.**

The internal mammary vessels accounts for 60% of the total breast blood supply. The lateral thoracic supply contributes about 30% of total breast vascularity ***(Skandalakis et al., 2006).***

The medial breast portion receives from the branches of the internal thoracic artery, especially in the 2nd and 3rd intercostal spaces. The lateral part is supplied by the lateral thoracic artery. Inferiorly, it is supplied by the anterior intercostal arteries, especially in the 4th and 5th intercostal

spaces. The superior portion receives perforators of the supra-clavicular and the thoracoacromial arteries. These vessels anastomose below the nipple areola complex (**NAC**), and then follow the connective tissue framework to penetrate the gland ***(Corduff & Taylor, 2003).***

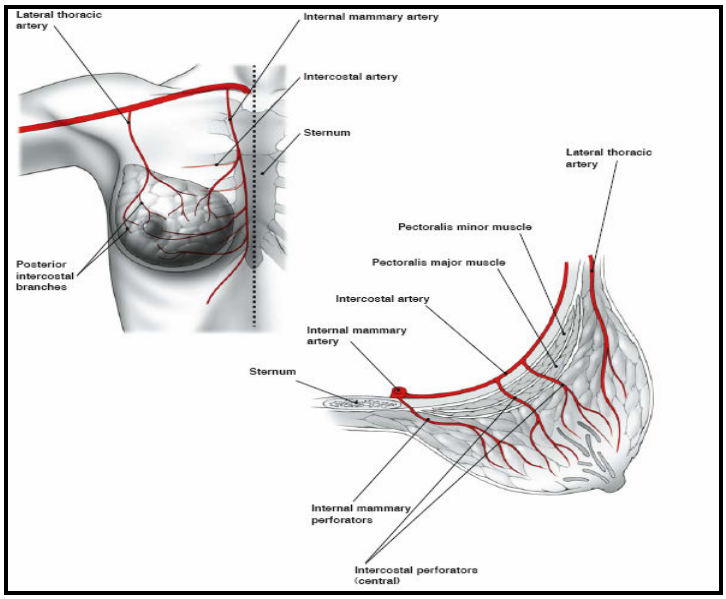

Figure (1.1): Arterial supply of the breast ***(Jatoi et al., 2006)***

Venous drainage:

The venous drainage of the breast is divided into two systems: the **superficial** and the **deep** system. The venous drainage of the breast is important not only because of the route of haematogenous metastatic spread from carcinomas, but also because of the lymphatic vessels generally follows the same course ***(Haagensen, 2006).***

A) The superficial venous system:

The superficial veins lie just deep to the superficial fascia. The superficial and deep veins anastomose with each other through the mammary gland and it may anastomose crossing the midline ***(Herniques, 2002).***

B) The deep venous system:

Venous drainage is mainly by deep veins that run with the main arteries to internal thoracic, axillary, subclavian veins and azygous system via the intercostal veins. The posterior intercostal veins anastomosis with the vertebral veins provides an important link and hence a pathway for metastatic spread to the bone ***(Mc Minn, 2004).***

Nerve supply to the breast:

The second to sixth intercostal nerves supply breast innervation. Lateral innervation is predominantly from the anterior rami of lateral cutaneous branches of the third to the sixth intercostal nerves. Medial innervation arises from the anterior cutaneous branches of the second to the sixth intercostal nerves. Nerve supply to the nipple is from the third, fourth, and fifth anterior and lateral cutaneous nerves. The fourth intercostal nerve is the most important nipple innervator ***(Skandalakis et al., 2006).***

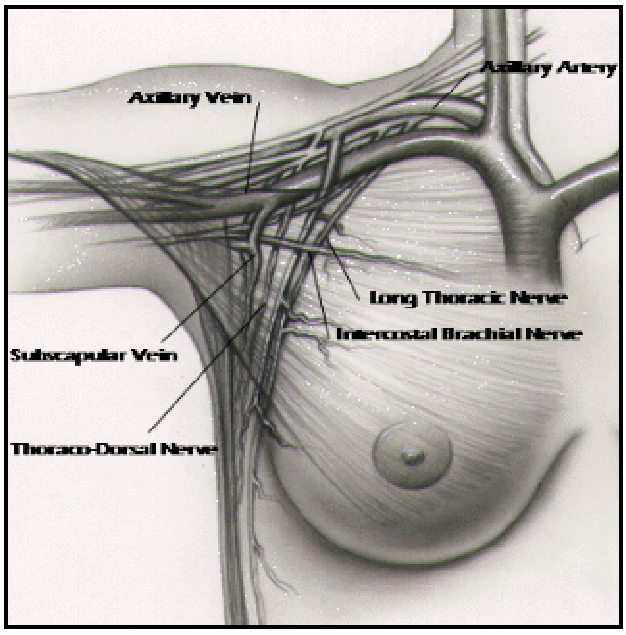

Figure (1.2): Nerve supply of the breast ***(Weiss, 2006)***.

Lymphatic Drainage:

Current understanding of the lymphatic system of the breast is derived mainly from the work of the anatomist Sappey in the 1850s ***(Sumai et al., 2007).***

The major groups of Haagensen are:

A. Axillary.

B. Internal thoracic (mammary). (Haagensen et al; 2002).

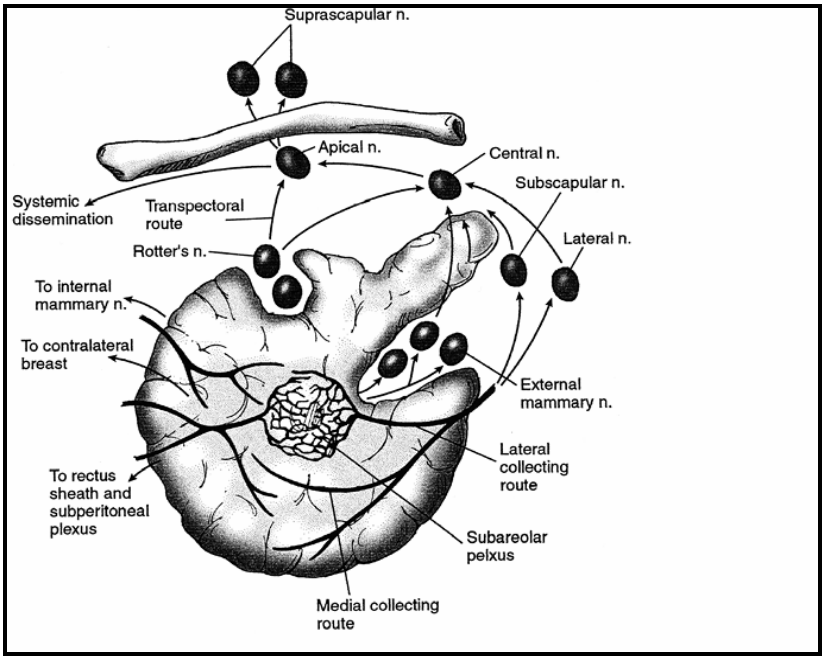

Figure (1.3): Schematic of the mammary organ identifying the position of lymphatic groups relative to the breast with illustration of the routes of lymphatic drainage. The clavicle represents the primary reference point. Level I lymph nodes include the external mammary (or anterior) axillary vein (or lateral) and scapular (or posterior) groups; level II, the central group; and level III, the subclavicular (or apical). The arrows indicate the routes of lymphatic drainage ***(Romrell & Bland, 2007).***

1) Axillary Drainage:

- **Group 1**: External mammary nodes (the anterior pectoral nodes.):

These lie along the lateral edge of the pectoralis minor, deep to the pectoralis major muscle, along the medial side of the axilla following the course of the lateral thoracic artery on the chest wall from the second to the sixth rib. Deep to the areola there is an extensive network of lymphatic vessels, the so-called subareolar plexus of Sappey. In the circumareolar region, large lateral and medial trunks receive much of the lymph from the breast parenchyma. The lateral trunk receives collaterals from the upper half of the breast and the internal trunk drains the lower part of the breast. These vessels pass around the lateral border of the pectoralis major muscle to reach the external mammary nodes.

- **Group 2:** Scapular nodes.

These lie on the subscapular vessels and their thoracodorsal branches. Lymphatics from these intercommunicate with intercostal lymphatic vessels.

- **Group 3:** Central nodes.

This is the largest group of lymph nodes; they are the nodes most easily palpated in the axilla, because they are generally larger in size. They are embedded in fat in the center of the axilla. When these nodes enlarge, they can compress the

intercostobrachial nerve, the lateral cutaneous branch of the second or third thoracic nerve, causing accompanying pain.

Group 4: Interpectoral nodes (**Rotter's nodes**).

These lie between the pectoralis major and minor muscles. Often there is a single node. They are the smallest group of axillary nodes and will not be found unless the pectoralis major is removed.

- **Group 5:** Axillary vein nodes.

This is the second largest group of lymph nodes in the axilla. They lie on the caudal and ventral surfaces of the lateral part of the axillary vein.

- **Group 6:** Subclavicular nodes.

These lie on the caudal and ventral surfaces of the medial part of the axillary vein ***(Blans & Vezerids, 2001).***

Haagensen considered them to be inaccessible unless the pectoralis minor muscle is sacrificed ***(Weiss, 2006).***

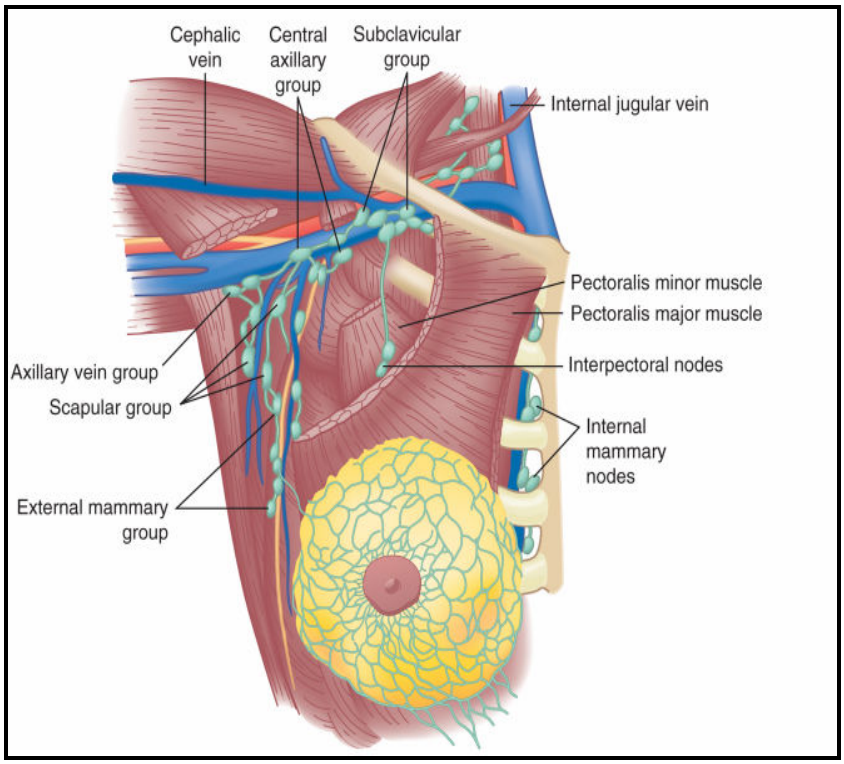

Figure (1.4): The Axillary Lymph Nodes ***(Donegan & Spratt, 2012)*.**

2) Internal Thoracic (Mammary) Drainage

Lymphatic vessels emerge from the medial edge of the breast on the pectoralis fascia. They accompany the perforating blood vessels, which, at the end of the intercostal space, pierce the pectoralis major and intercostal muscles to reach the internal thoracic nodes. These nodes also receive lymphatic trunks from the skin of the opposite breast, the liver, the diaphragm, the rectus sheath, and the upper part of the rectus abdominis. The nodes, about four to five on each side, are small and are usually in the fat and connective tissue of the intercostal

spaces. The internal thoracic trunks empty into the thoracic duct or the right lymphatic duct. This route to the venous system is shorter than the axillary route ***(Skandalakis et al., 2006).***

Since dissection of the internal mammary nodes is not done today, ***(Scatarige et al., 2010)*** advised lateral chest radiography, computed tomography, high-resolution sonography, magnetic resonance imaging, and radionuclide lymphoscintigraphy.

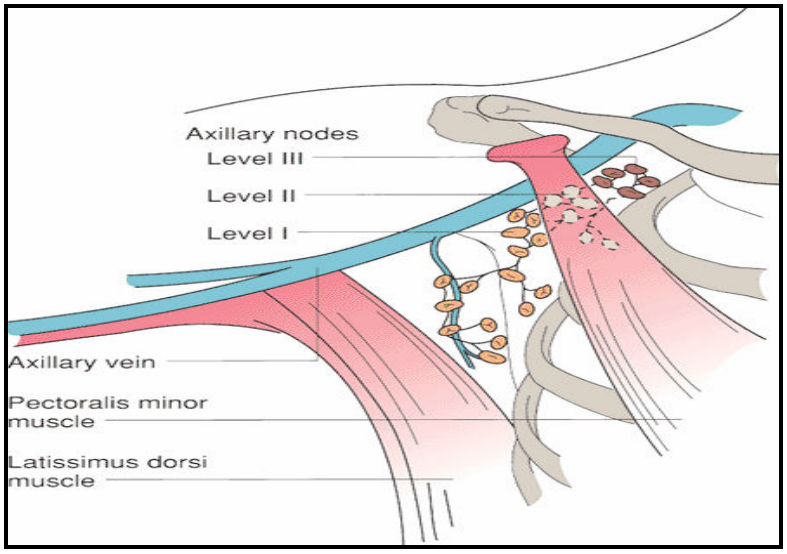

Figure (1.5): The axillary lymph nodes are divided into three levels by the pectoralis minor muscle ***(Sacre, 2006).***

The level I nodes are inferior and lateral to the pectoralis minor, the level II nodes are below the axillary vein and behind the pectoralis minor, and the level III nodes are medial to the muscle against the chest wall ***(Sacre, 2006).***