INTRODUCTION

Breast cancer is the most common malignancy and leading cause of cancer –related death in women in the western world ***(Jemal et al., 2003)***.

However, the events leading to the transition from normal to cancerous epithelium are still not fully understood. As our understanding of cancer genetics increases ***(Ding and Celina, 2006).***

Tow genes linked to breast cancer have been identified. These are known as breast cancer genes BRCA1 and BRCA2. Mutation in the BRCA1/2 genes are rare in most populations (with a prevalence of 0.3%) but they are believed to have high penetrance. These mutations account for about 5-10% of all breast cancers in general population ***(Chang– Claude, 2004)***.

Women carrying gene-line Mutations in BRCA1 or BRCA2 are at risk for early- onset breast cancer. Such women currently receive annual mammograms beginning at age 25-30 years ***(Jenkintown, 2005).***

Breast cancer is the commonest malignancy in women worldwide; more than 1million new cases were diagnosed in 2000 ***(IARC, 2002).***

Between 1975-1990, Asia and Africa have experienced a more rapid rise in the annual incidence rates of breast cancer than North America and Europe ***(Sasco, 2001).***

In the united states the incidence is lower among African American women (19.4/100 000) than among Caucasian women (141.1/100 000) ***(Smiga et al., 2006).*** In Nigeria the prevalence of breast cancer is 116 per 100 000 ***(Adebamowo and Ajayi, 2000).*** In Australian women more than 12 000 cancer breast were diagnosed with the disease and almost 2 600 died from it ***(Australian Institute of Health and Welfare, 2006).***

In Pakistan, reports breast cancer as the most common cancer (34.6% of cancer cases) among females ***(Bhurgri, 2004).*** About 2 100 new cases of breast cancer and 800 death are registered each year in Norway. In India, a death rate of one in eight women has been reported due to breast cancer ***(Sheshadri and Kandaswamy, 2006).***

Early detection is the most effective way to reduce mortality, and currently a screening program based on mammography is considered the best method for early detection of breast cancer ***(Sheshadri and Kandaswamy, 2006).***

The increasingly early detection of breast cancer has resulted in significant improvements in the rate of cure in this disease ***(Claudia and Berman, 2007)***.

The diagnostic and prognostic markers of breast cancer are limited. Thus there is an urgent need for identification of novel molecular markers that can detect the neoplastic process at its earliest phases before cancer develops. Such markers would assist in predicting individual risk for breast cancer, as well as constitute the basis for preventative targeted therapies ***(Ding and Celina, 2006)***.

Mammography has been proven to detect breast cancer at an early stage and, when followed up with appropriate diagnosis and treatment, to reduce mortality from breast cancer. Screening MRI is recommended for women with an approximately 20-25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease ***(Saslow et al., 2007)***.

AIM OF THE WORK

To declear updated methods of early detection of women at high risk of developing breast cancer and effect of early detection on management of breast cancer.

EMBRYOLOGY

Embryologic development of the mammary gland consists of a series of highly ordered events involving interactions among a number of distinct cell types. These interactions are regulated by an array of systemic and local factors such as growth factors and hormones ***(McCarty et al., 1990).***

The epithelial of the ducts and acini of the breast is developed from ectoderm and the supporting tissue is derived from the mesenchyme ***(McGregor, 2003).***

During the fourth week of gestation, paired ectodermal thickenings termed mammary ridges or milk lines develop on the ventral surface of the embryo and extend in a curvilinear fashion convex towards the midline from the axilla to the medial thigh. This is the first morphological evidence of mammary gland development. In the normal human development, these ridges disappear except at the level of the fourth intercostals space on the anterior thorax, where the mammary gland subsequently develops ***(Revis et al., 2006).***

Each breast develops when an ingrowth of ectoderm forms a primary tissue bud in the mesenchyme. The primary bud, in turn, initiates the development of 15 to 20 secondary buds. Epithelial cords develop from the secondary buds and extend into the surrounding mesenchyme. Major (lactiferous) ducts develop, which opens into a shallow mammary pit. During infancy, a proliferation of mesenchyme transforms the mammary pit into a nipple. If there is failure of a pit to elevate above the skin level, an inverted nipple results. This congenital malformation occurs in 4% of infants. At birth, the breasts are identical in male and females, demonstrating only the major ducts. Enlargement of the breast may be evident and a secretion, referred to as witch's milk, may be produced. These transitory events occur in response to maternal hormones that cross the placenta ***(Bland et al., 2005).***

Congenital breast malformations range in severity from the relatively minor to major chest wall deformities. Minor malformations may not even be recognized, while major deformities may cause significant functional, psychological, and aesthetic concerns. The affected individual may present for consultation at any ages, often early in childhood as a result of parental concern. These malformations generally fall into 1 of 2 categories, the presence of supernumerary breast tissue or the absence or underdevelopment of breast tissue ***(Revis et al., 2006).***

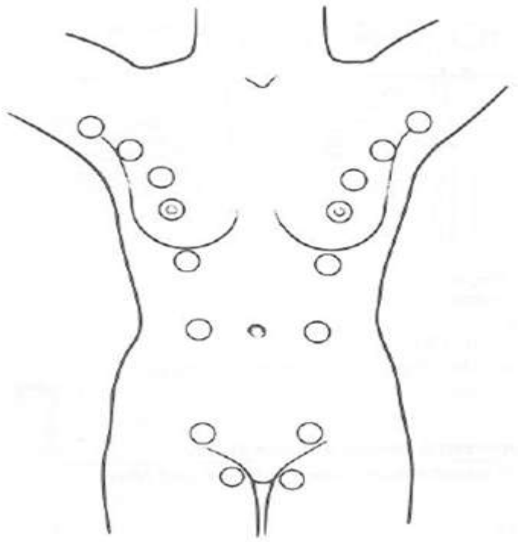

Figure (1): Sites of accessory breast (Mammary line) ***(Hans, 2006).***

An extra breast (polymastia) or extra nipple (polythelia) occurs in approximately 1% of the population. It may be an inheritable condition. Supernumerary nipples are slightly more common in males than in females. Extra breasts or nipples most commonly occur along the milk line, usually just underneath the normally located breasts or nipples, however, they have also been noted in ectopic sites such as the back or the buttock. Accessory or ectopic breast tissue responds to hormonal stimulation and may cause discomfort during menstrual cycles. These tissues have also been reported to undergo malignant transformation and should be removed ***(Arca et al., 2008).***

Poland's syndrome is an uncommon congenital chest wall deformity characterized by unilateral absence of the sternal head of the pectoralis major muscle, deficiency of the breast and nipple, chest wall deformity and abnormalities of the upper extremity including finger-shorting and syndactyly ***(Sainsbury, 2006).***

Gross Anatomy

The breasts are specialized accessory glands of the skin that are capable of secreting milk. They are present in both sexes. In males and immature females, they are similar in structure. The nipples are small and surrounded by a colored area of skin called the areola. The breast tissue consists of little more than a system of ducts embedded in connective tissue that does not extend beyond the margin of the areola ***(Snell, 2004).***

Growth and branching of the mammary glands progress slowly during the prepubertal years. Development of the mammary glands dramatically increases at puberty with further branching of ducts, formation of acini buds, and a dramatic proliferation of interductal stroma. The nulliparous breast has a typical hemisphere configuration with distinct above the nipple. At the time of pregnancy the breast achieve complete structural maturation and full functional activity. During pregnancy, the intralobular ducts develop rapidly, forming buds that become alveoli, and the stromal glandular proportions in the breast are reversed. Thus with multiparity and the hormonal stimulation that accompanies pregnancy and lactation. The organ assumes a larger and more pendulous form and increases in volume and density. During the postmenopausal years, both the ductal structures and connective tissue of the breasts are markedly diminished in size. With the aging breast assumes a flattened, flaccid and more pendulous configuration with decreased volume ***(Bland et al., 2005).***

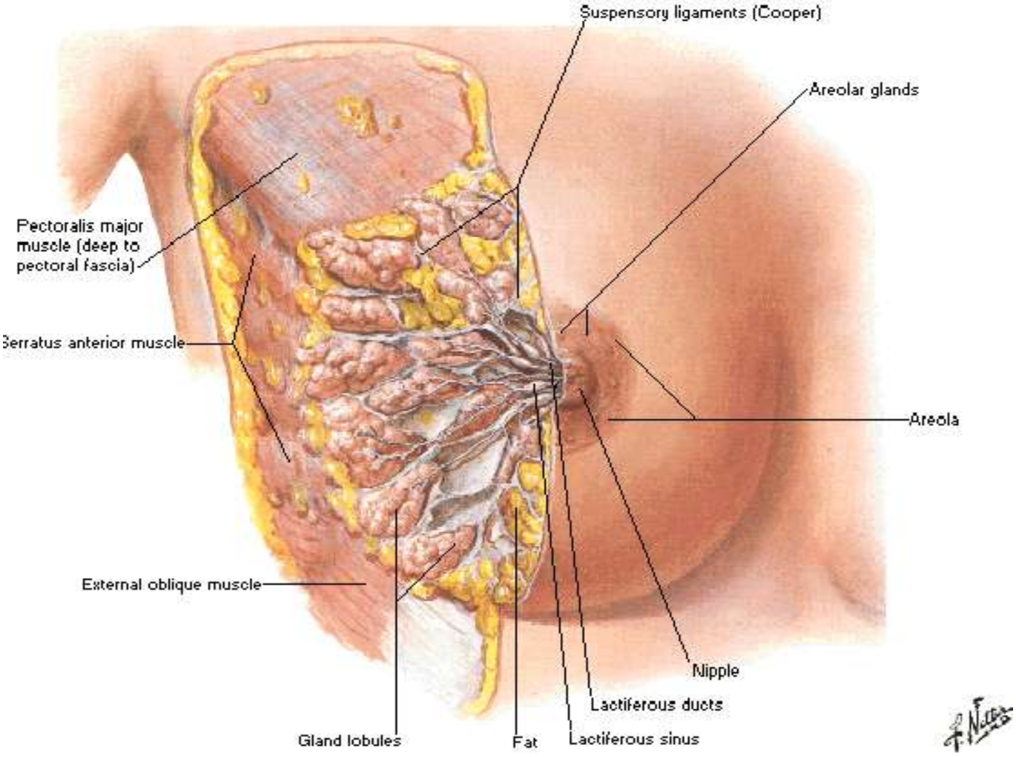

Figure (2): Anatomy of the breast ***(Hans, 2006).***

The protuberant part of the human breast is generally described as overlying the 2nd and the 6th ribs and extending from the lateral border of the sternum to the anterior axillary line. Actually a thin layer of mammary tissue extends considerably farther from the midline to the edge of latissimus dorsi ***(Saunders and Baum, 2000).***

The breast is located within the superficial fascia of the anterior chest wall. Two third of the base of the breast lies anterior to the pectoralis major muscle, the remainder lies anterior to the serratus anterior muscle. A small part may lie over the aponeurosis of the external oblique muscle. In about 95% of women, here is a prolongation of the upper lateral quadrant towards the axilla, breast tail. This tail of (*Spence*) of breast tissue enters a hiatus of (langer) in the deep fascia of the medial axillary wall. This is the only breast tissue found beneath the deep fascia ***(Skandalakis et al., 2000).***

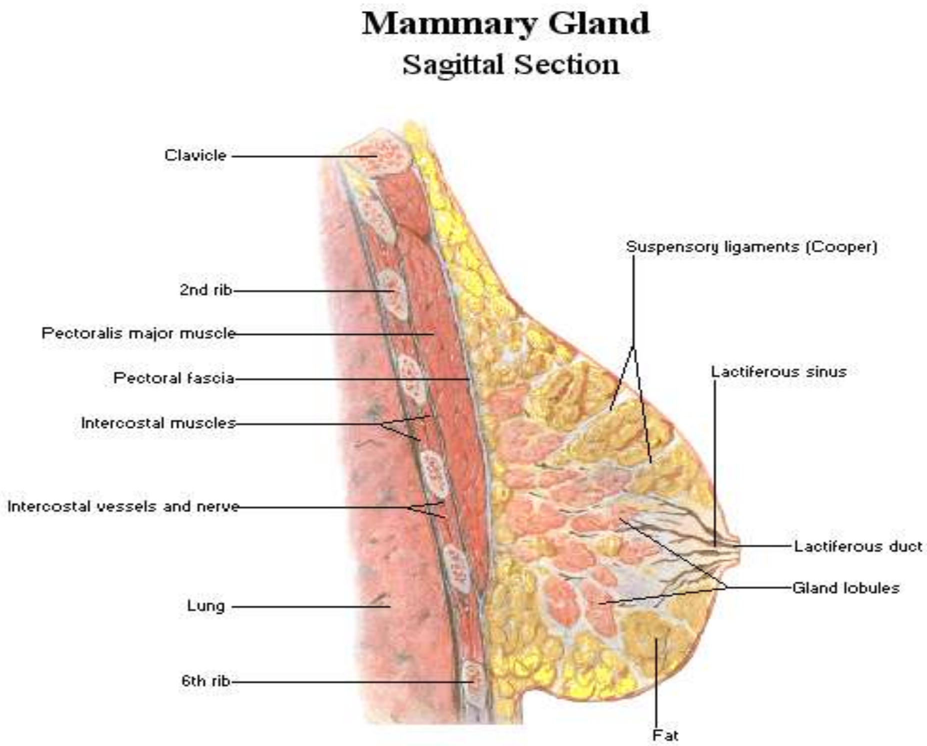

Figure (3): Anatomy of the breast ***(Hans, 2006).***

Microscopic Anatomy

The breast is composed of a system of ducts and lobules surrounded by connective tissue stroma. The ductal system contains numerous lobules with acini. Each lobule feeds into a terminal duct, which, in turn, feeds into a segmental duct. The segmental ducts ultimately feed into collecting ducts, and about

15-20 of these converge under the areola on to the surface of the nipple through separate orifices. The connective tissue which surrounds the lobules is dense whereas intralobular connective tissue has a loose texture and contains variable amounts of adipose tissue, which contributes largely to the increase in breast size at puberty. Fibrous condensations of stromal tissue extend from the ducts to the dermis. These are often well developed in the upper part of the breast as *suspensory ligaments of cooper* which assist in supporting the breast tissue ***(Collins et al., 2005).***

In mature resting breast, major ducts are lined with two layers of cuboidal cells is present. The bases of these cells are in close contact with numerous myoepithelial cells of ectodermal origin. The duct lining is replaced by keratinized stratified stratified squamous epithelium close to the nipple. In the inactive breast, the epithelium is sparse and consists primarily of ductal epithelium. In the early phase of menstrual cycle, minor ducts are cord lik with small lumina. With estrogen stimulation at the time of ovulation, alveolar epithelium increase in height, duct humina become more prominent and some secretions accumulate. When the hormonal stimulation decreases the alveolar epithelium regresses ***(Bland et al., 2005).***

Blood Supply

The blood supply of the breast is derived from:

1. The lateral thoracic artery, from the 2nd part of the axillary artery.

2. The perforating cutaneous branches of the internal mammary to the 2nd, 3rd and 4th spaces.
3. The lateral branches of the 2nd,3rd and 4th posterior intercostals arteries (***McGregor, 2003***).

A. Axillary artery
B. Axillary vein
C.Internal mammary artery
D. .Internal mammary vein
E.Intercostal veins
F.Intercostal arteries

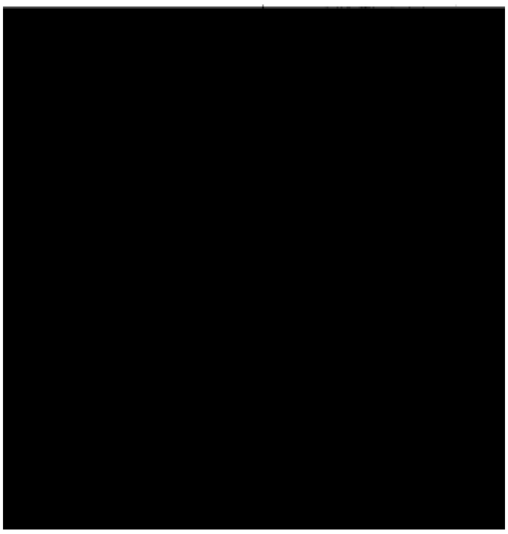

Figure (4): Blood supply of the breast ***(Hans, 2006).***

The 2nd, 3rd and 4th anterior intercostals perforating arteries and branches of the internal mammary artery pass in the breast as medial mammary arteries. The veins of the breast follow the course of the arteries with venous drainage being to wards the axilla. The superficial breast veins have extensive anastomoses that may be evident through the overlying skin. Around the nipple, these superficial veins form an anastomotic circle, the circulus venosus. Veins from this circle and from deeper aspects of the gland drain blood to the periphery of the breast, thereafter into vessels that terminate in the internal mammary, axillary and internal jugular veins. The posterior intercostals veins lie in direct continuity with vertebral plexus of veins (Boston's plexus) which invests the vertebral and extends from the base of the skull to sacrum may provide a route for breast cancer metastasis to the skull, vertebrae, pelvic bones and central nervous system ***(Bland and Vezeridis, 2006).***

Lymphatic Drainage

The lymphatics of the breast are thin walled, valveless vessels that drain unidirectionally except when obstructed by inflammatory or neoplastic disease. The superficial subareolar lymphatic plexus drain primarily the skin of the breast and the nipple and areola, in addition to some of the central portion of the gland. This plexus is interconnected with the deep lymphatic plexus which drains most of the breast parenchyma ***(Morrow and Khan, 2006).***

Injections of radioactively labeled have demonstrated that about 97% of the lymphatic flow from the breast drains dirains directly into the axillary lymph nodes. The axillary space is bordered by the axillary vein superiorly, the latissimus dorsi laterally and the serratus anterior medially. The pectoralis major lies anterior to the axillary space and the subscapularis comprises its posterior wall. Structures of clinical importance within this space include the long thoracic nerve, which innervates the serratus anterior, the thoracodorsal neurovascular bundle which innervates and supplies blood to the latissimus dorsi and the intercostobrachial nerves which are sensory to the upper inner aspect of the arm. The axillary nodes are embedded in fat and variable in number.

Surgeons have traditionally divided the axillary nodes into three levels:

- Level I nodes, inferior and lateral to the pectoralis minor.
- Level II nodes, behind the pectoralis minor and inferior to the axillary veins.
- Level III nodes, medial to the pectoralis minor and against the chest wall.

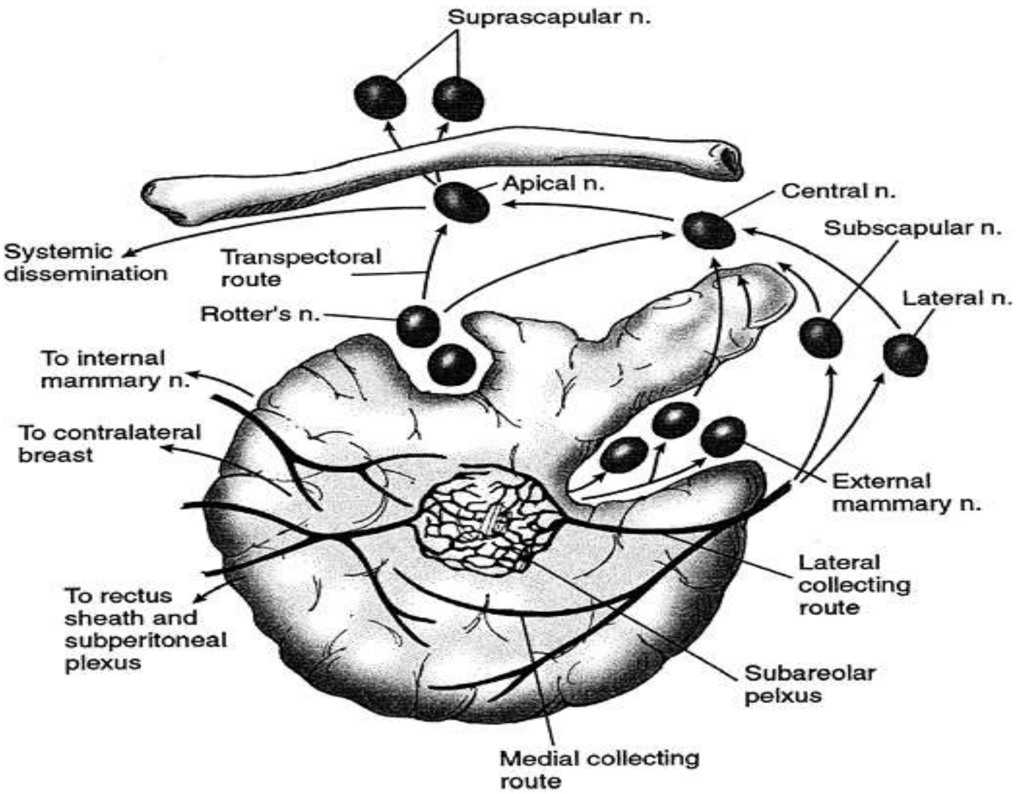

Figure (5): Lymphatic drainage of the breast ***(Hans, 2006).***

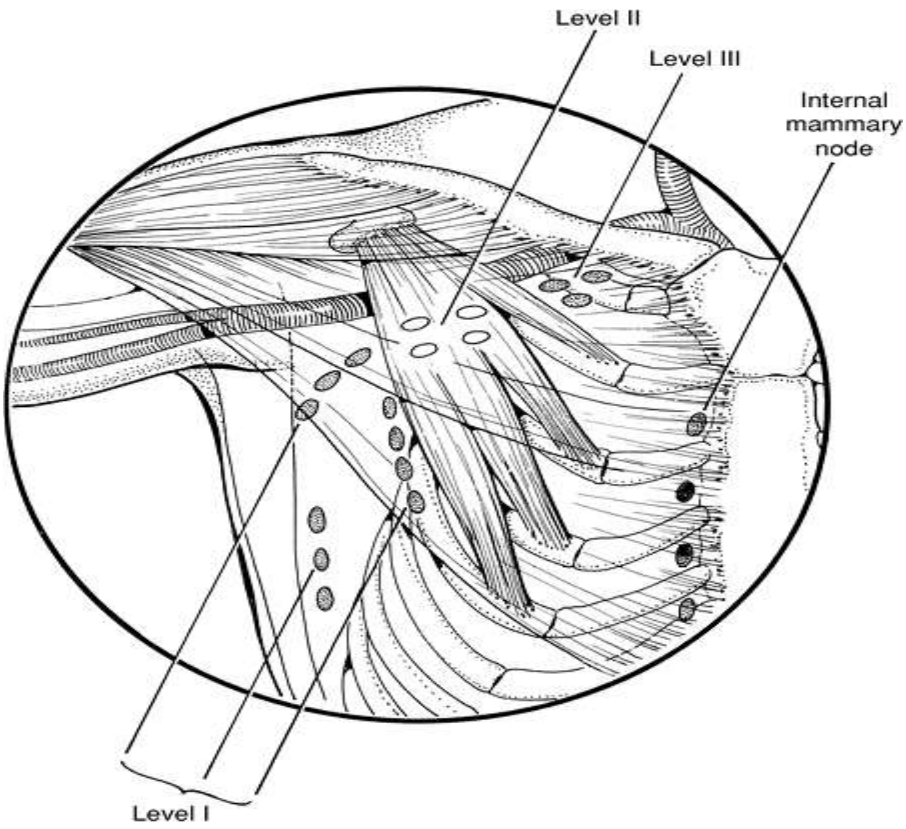

Figure (6): Lymphatic drainage of the breast ***(José, 2006).***

The interpectoral (or Rotter's) nodes are located between the pectoralis major and minor muscle along the lateral pectoral nerve. Involvement of this node group in the absence of axillary metastases is extremely rare and thus they are of limited clinical significance. The supraclavicular nodes are contiguous with the apex of the axilla. Metastaic involvement of this nodal group is occasionally seen. The internal mammary nodes are located in the first six intercostal spaces within 3cm of the edge of the sternum. The highest concentration of the internal mammary nodes is found in the first three intercostals spaces ***(Marrow and Khan, 2006).***