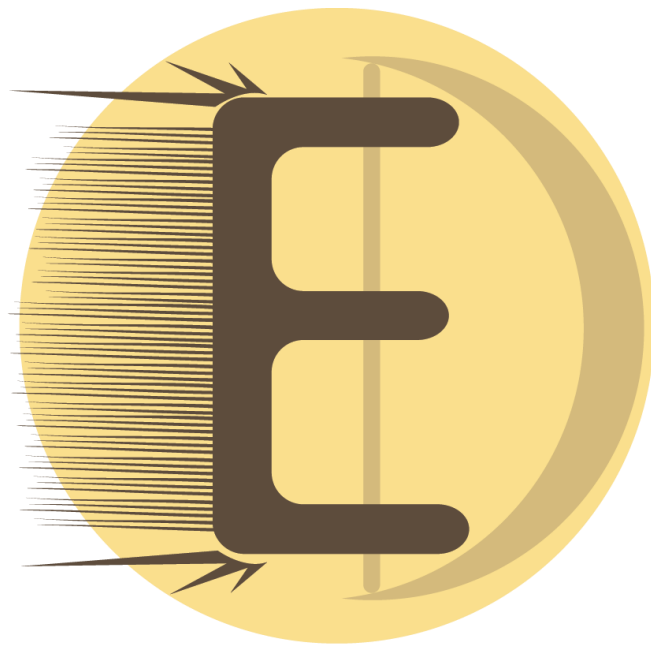


Breast Cancer: A Literature Review



EXPRESS DISSERTATION

Table of Contents

1.0. Background	3
2.0. The Human Breast	3
2.1. Anatomy of the Breast.....	3
2.2. Development and differentiation of the female breast	5
3.0. Risk factors for breast cancer.....	8
3.1. Genetic Risk Factors	8
3.2. Hormonal Factors.....	9
3.3. Breast Density	10
3.4. Pre malignant lesions	10
3.5. Pathogenesis and classification of breast cancer.....	11
3.6. Tumour markers	12
3.7. Prognostic and predictive factors	14
Estrogen and Progesterone receptors	14
HER2/neu -Human Epidermal Growth Factor Receptor 2	15
Urokinase-Type Plasminogen Activator (uPA) and Plasminogen Activator Inhibitor type 1 (PAI-1)	15
Genetic profiling.....	16

EXPRESS DISSERTATION

1.0. Background

Worldwide, of all the invasive cancers, breast cancer is the most common. As per recent statistics, it comprises nearly 16% of all female cancers and 23% of invasive cancers among women (World Cancer Report, 2008, http://www.iarc.fr/en/publications/pdfs-online/wcr/2008/wcr_2008.pdf). In 2008, 13.7% of cancer deaths in women and 6% of all cancer deaths were caused by breast cancer (World Cancer Report, 2008). In the United States each year, about 180,000 women are diagnosed with breast cancer and nearly 6% of women are at the risk of developing it (Martin and Weber, 2000; Cutler *et al*, 2009). The risk of breast cancer in a lifetime in Australian women until the age of 75 is 1 in 11 (Cutler *et al*, 2009). It has been noted to be the most common cancer in Australian women aging between 34 and 75 years. In 2005, approximately 12,000 fresh cases of invasive breast cancer were detected in Australian Association of Cancer Registries and Australian Institute of Health (AACR, 2008) and Welfare (AIHW).

2.0. The Human Breast

2.1. Anatomy of the Breast

The breasts are apocrine glands, which following full term pregnancy produce and secrete milk to nourish the offspring. A basic overview of breast anatomy is given in figure 1. The breast comprises of glandular tissue, which is embedded in fatty tissue and is supported by fibrous connective tissue and Cooper's ligaments (suspensory ligaments). The lateral and anterior branches of the intercostal nerves (4th, 5th and 6th) innervates the peripheral nervous system of the breast, whereas the nipple-areola complex is innervated by the thoracic spinal nerve 4 (T4). Blood is supplied to the breast tissue by blood and lymph vessels that also aid in eliminating wastes into the axillary lymph nodes which are located in the armpit and upper chest. The lobular alveolar structure, which consists of alveoli, is the glandular component of the breast tissue that forms groups called lobules. When lactation occurs, milk that has been produced in the alveoli is drained into the mammary ducts that further are connected to lactiferous sinuses and ducts. Further, the mammary lactiferous ducts connect to the nipple that secretes the milk (Ramsay *et al*, 2005).

The two types of epithelial cells that comprised the glandular tissue of the breast are myoepithelial cells and luminal epithelial cells. The myoepithelial cells surround the luminal epithelial, which may be cuboidal or columnar, which surround the inner walls of ducts and

alveoli (Emerman and Vogl, 1986). The myoepithelial and luminal cells ascend from myoepithelial-restricted and luminal-restricted progenitor cells correspondingly (Stinglet *et al*, 2001, Stinglet *et al*, 2005). Progenitor cells that are capable of producing both luminal myoepithelial and cells have also identified (Emerman and Vogl, 1986, Stinglet *et al*, 2005). Basal clear cells, which are the precursors of myoepithelial cells have also been found lactiferous ducts in addition to the lobular-alveolar structures in the breast, between the luminal and myoepithelial class (Smith *et al*, 1984).

Myoepithelial cells that have a basket like appearance act as a sheath around the ducts in the lobular-alveolar structure. Myoepithelial cells have been reported to possess contractile ability, due to which these cells enlarge during pregnancy and contract during lactation on the when stimulation of the hormone oxytocin. When the myoepithelial cells contract, it leads to the secretion of milk from the alveoli into the lactiferous ducts, which finally leads to the nipple (Emerman and Vogl, 1986).

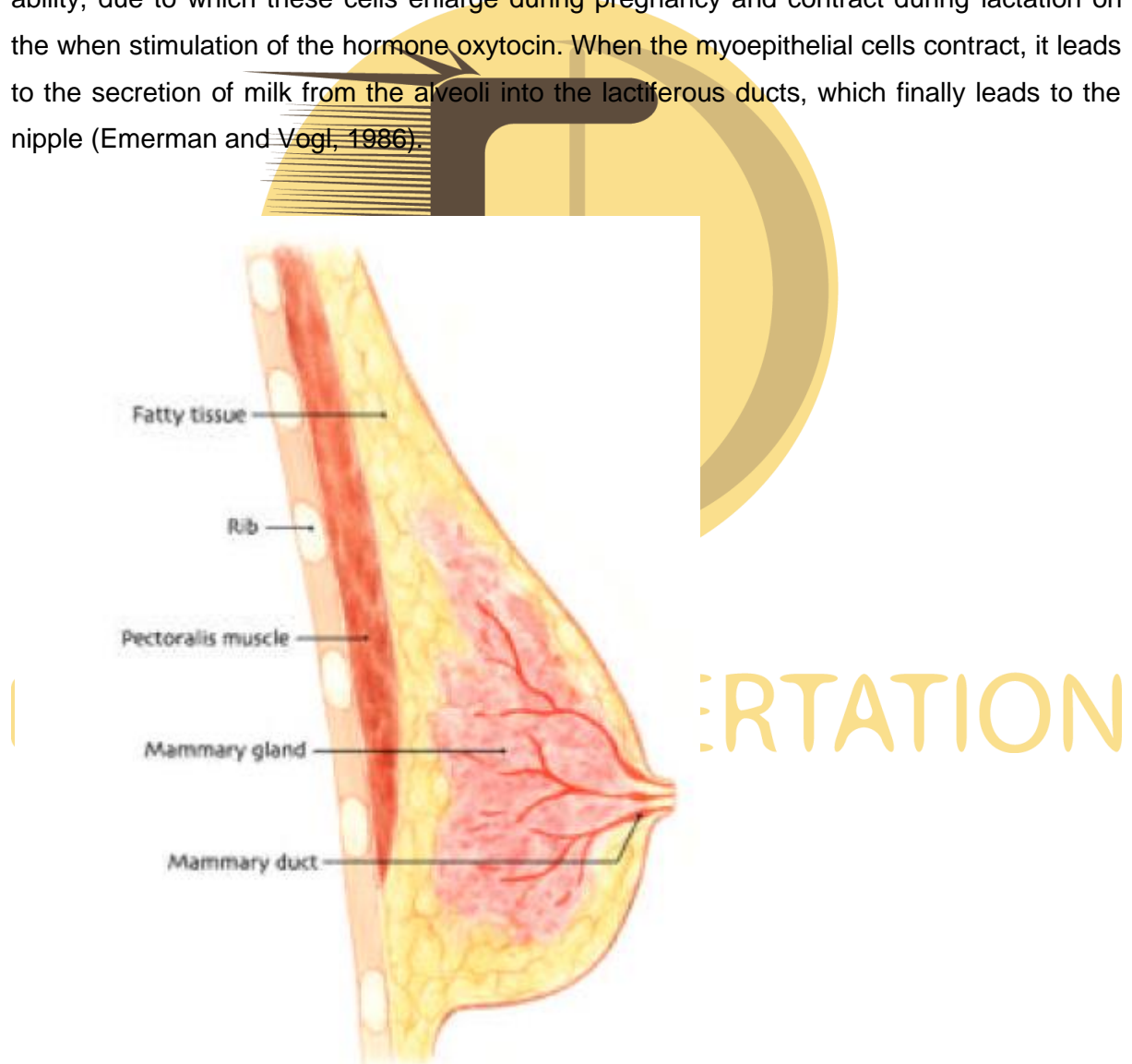


Figure 1: Anatomy of breast

Source: (University of Michigan health system, 2012)

2.2. Development and differentiation of the female breast

From infantile growth to puberty, pregnancy, lactation, and finally post-menopausal regression the breast, which is a bilateral organ in the females, undergoes vivid changes in terms of shape, size, function (Tanner, 1962; Vorherr, 1974). According to Chu *et al*, (1999) and Jemalet *al*, (2003) the most common malignancy among women is breast cancer. This makes it essential to acquire a complete understanding of the effects that reproductive events and hormonal changes cause in the various stages of breast development (MacMohan, 1970; Russo and Russo, 1996). Breast is a hormone dependent organ as its growth and differentiation depends on hormones progesterone and estrogen. As a result they are considered significant in the development and progression of breast cancer (Pike *et al.*, 1993, Colditz, 1995).

Human breast development, which is initiated in the embryonic stage, lasts till the age of 35. The hormones activated in puberty influence the mammary glands. The final major change to occur in breasts is the shrinkage or involution of the milk ducts. As noted by Clark *et al.*, (1996) the gradual involution or shrinking of the mammary glands typically begins around regression, which is roughly around the age of 35. During puberty, lobule formation and growth spurt occur, which but complete differentiation and development occurs when the full term of first pregnancy ends (Russo and Russo, 1987). Studies have revealed that early parity is inversely related to the risk of breast cancer (MacMohan, 1970; Russo and Russo, 1996).

The mammary gland parenchyma, in the embryonic stage, grows from a single epithelial ectodermal bud. Right when the pregnancy begins and the embryo is in the uterus, the mammary glands begin to develop. Mammary gland development, in the intrauterine environment, takes place in successively in phases till the gestational age of 40 weeks, which is when the last vesicle stage occurs and the foetus has a crown rump length of > 360 mm. Because of the lacking developed lobules, the end vesicle stage is not completely differentiated (Sakakura, 1987).

The rudimentary mammary gland along with the glandular tissue as well as the surrounding stroma begins to develop with the advent of puberty (Tanner, 1962; Vorherr, 1974). This causes an increase in the amount of fatty and fibrous tissue in the stroma. Repeated growth primary and secondary ducts occurs which results in glandular enhancement. Division is believed to be sympodial (along a main axis) and dichotomous (by bifurcation), which results

in the formation terminal ductal lobular unit (TDLU) composed structural unit composed of virgin lobule. Generally after 1 or 2 years after menarche, the breast begins to differentiate. Mammary development that is induced by ovarian hormones during the course of a menstrual cycle doesn't ever fully return to the initial point of the previous cycle. Thus, with each ovulatory cycle slight mammary development occurs, along with the budding of new structures that goes on until the age of 35 years (Russo and Russo, 1987).

The breast tissue of a non-pregnant, normally menstruating adult woman contains three distinguishable lobules: Lob 1 which are immature lobules, Lob 2 and Lob 3 which are more developed lobules and are formed as an outcome of the gradual sprouting of fresh ductules. Around the terminal duct, Lob 3 is characterised by a minimum of 80 ductules and Lob 2 has an average of 47 ductules. With the progression of branching, the size of individual ductules becomes smaller nevertheless, the overall size of the more developed lobule increases (Russo and Russo, 1987).

Maximum development of the breast ensues in two distinct phases during pregnancy. The initial stage is distinguished by profuse branching and ductal lengthening which happens because of active cell proliferation occurring at the ductal tree on its distal end. This is complemented with the rapid increase in the formation of new ductules that lead to progression of Lob 2 to Lob 3. The degree of lobule formation and the intensity of budding and exceeds that is in the virgin breast. When a girl is in puberty, during the breast development stage also known as thelarche, the growth sprouting and development of breasts is promoted by female sex hormones. During this time, the mammary glands grow in volume and size, and ordinarily rest on the chest, this type of breast is known as virgin breast (Wood et al., 2008). The secretory activity is in the fully differentiated Lob 4 is facilitated by the development of ductules and acini, which is characteristic to this stage.

After postpartum withdrawal of sex steroids and placental lactogen, lactation starts, this appears to avert prolactin's action on the mammary epithelium (Russo et al, 1992). Morphological changes seldom occur in the mammary gland during lactation. Milk is constantly produced and secreted into the mammary acini and ductal system providing it is extracted from the mammary gland on a regular basis. Further inhibitory effect is caused on milk synthesis by weaning. A series of involution changes follow next in the mammary gland, which include multifocal asynchronous process of decrease in the size of the secretory epithelial cells, inhibiting their secretory activity (Russo and Russo, 1987; Russo *et al*, 1992). Two complementary mechanisms mediate post-lactational. First is collapse of acinar structures brought on by cell autolysis, and the second is renewal of proliferation and

budding in the terminal tubules with the regeneration of perilobular and periductal connective tissue and disintegration of lobules. As compared to nulliparous breast, the parous organ holds more glandular tissue, until menopausal involution sets in (Russo and Russo, 1987; Russo *et al*, 1992).

When over 99% of the follicles existent in the ovaries are exhausted by atresia or ovulation, menopause occurs. The most distinctive sign of menopause is the cessation of menses (amenorrhea), which is caused by the lowering or extinguished levels of ovarian hormones like oestrogen and progesterone, which put an end to endometrial. In both nulliparous and parous women the breasts undergo a regressive phenomenon after menopause. This regression is morphologically observable in the breast as a decline in the number of Lob 3 and Lob 2 structures and a simultaneous increase in the number of Lob 1 structures. By late 40s or early 50s, the breast predominantly contains type 1 lobules in case of both parous and nulliparous women (Russo and Russo, 1987; Russo *et al*, 1992).

Lob 1 is the predominant breast structure in nulliparous women and accounts for about 65 to 80% of the entire lobular component and their comparative percentage is not dependent on age. Lob 2 represents about 10 to 35% of the total lobular components of the breast, whereas Lob 3 represents just 0 to 5% of the entire lobular structures. However, the predominant lobular structure in premenopausal parous women is Lob 3 and it makes up nearly 70 to 90% of the entire lobular component. After menopause, there is a decline in the number of Lob 3 and the relative proportion of all the three lobular structures extant in parous women, resemble that of nulliparous women. This implies that early parous women, women who have completed a full term pregnancy, undergo lobular differentiation, which was apparent at a younger age, whereas when comparing nulliparous women, women who have not had a pregnancy, rarely attain the Lob 3 stage and neither the Lob 4 stages in extension (Russo *et al*, 1992). The following figure, figure 2, illustrates these differences observed in the cycle of breast development

CYCLE OF BREAST DEVELOPMENT AND DIFFERENTIATION

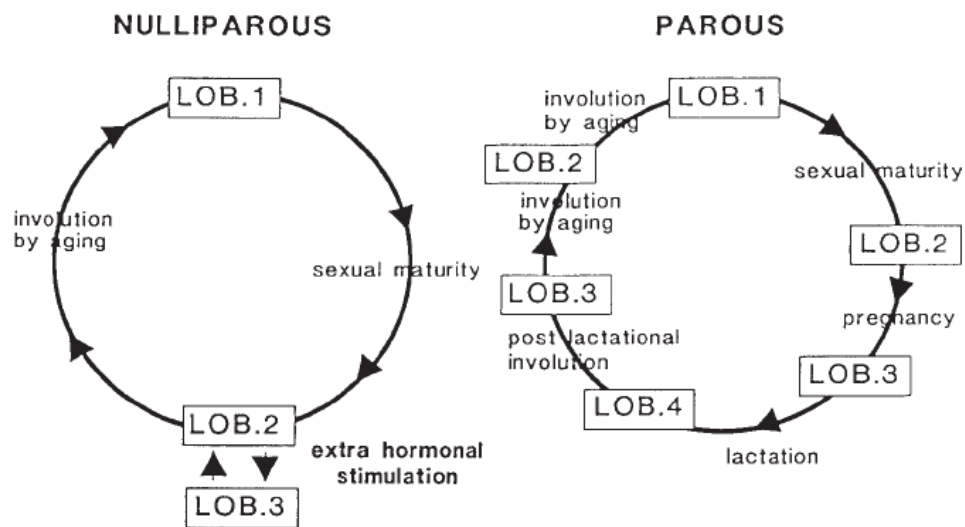


Figure 2. Cycle of breast development and differentiation in nulliparous and parous women. Adapted from Russo, et al. 1992.

3.0. Risk factors for breast cancer

A multifactorial disease, breast cancer, is caused by the interaction of environmental and genetic factors. Mentioned below are the risk factors for breast cancer

3.1. Genetic Risk Factors

As per Miki et al. (1994) and Wooster et al. (1995), in the perspective of large multiple families, localized on chromosome 17 and 13 respectively, *BRCA1* and *BRCA2* are the most significant breast cancer vulnerability genes. 5% of total breast cancer, 25% - 40% of familial breast cancer and 20% of total ovarian cancers are accounted for by mutations in these genes (Chen et al., 2006; Oldenburg et al., 2007). A meta-analysis of 22 hospital-based and population-based studies indicates that the risk of breast cancer at age 70 was 65% and 45% respectively for *BRCA1* and *BRCA2* mutation carriers (Antoniou et al., 2003) which is compare to the risk for uterine or cervical cancer is far higher despite of proofs of BRCA being related to it (Kadouri et al., 2007). Additionally, other inherited cancer susceptibility syndromes, like Cowden disease [*PTEN* (phosphatase and tensin homolog) mutations], Li-Fraumeni syndrome [*TP53* (tumour protein p53) mutations], hereditary diffuse cancer

syndrome [*CDH1* (cadherin 1) mutations], and Peutz-Jeghers syndrome [*STK11/LKB1* (serine/threonine kinase 11) mutations] show breast cancer as part of their clinical presentation (Martin and Weber, 2000). Although 5%- 10% of all cases account for hereditary breast cancer, under 25% of the hereditary cases are related to germline mutations found in the breast cancer susceptibility genes that have been identified till date (Bradbury and Olopade, 2007; Stratton and Rahman, 2008). Smith *et al* (2006) conducted a genome wide linkage analysis by using a wide number of families with several cases of breast cancer, who did not have mutation in *BRCA1* and *BRCA2*. Even though the study did not draw any added loci for breast cancer susceptibility, it suggested the existence of breast cancer susceptibility genes that had extra high-penetrance account for a slight proportion of the extra familial risk (Stratton and Rahman, 2008).

3.2. Hormonal Factors

Studies have recognized that continued exposure to oestrogen increases the risk of breast cancer being developed (Bogget *et al*, 1987; Pike *et al*, 1979) whereas reduced exposure is thought to be shielding (Hulka, 1997). Factors that heighten the number of menstrual cycles, like nulliparity, late menopause and early menarche are thought to heighten the risk of breast cancer because of extended exposure to ovarian hormones (Trichopoulos *et al*, 1972; Kampert *et al*, 1988; White, 1987). Protection against breast cancer can be achieved by longer lactation period and moderate levels of exercise that reduce the number of ovulatory cycles (Bernstein *et al*, 1994; Yuan *et al*, 1988; Holmes *et al.*, 2005). The role of HRT (postmenopausal hormone replacement therapy) is unclear in the development of breast cancer. Although the possibility of breast cancer because of HRT seems to be comparatively small, it has been noted in studies that continuing use may increase the possibility of breast cancer being developed (Agarwal and Judd, 1999; Steinberg *et al*, 1991). Collins (2005) in his review identified the comparative risk of breast cancer incidence against using specific hormones. In four random trials including 12 643 women, the average risk reported of invasive breast cancer by way of estrogen use was 0.79 [95% confidence interval (95% CI) = 0.61–1.02]. Whereas, in four random trials including 19 756 women, the average risk of breast cancer by way of estrogen–progestin use was 1.24 (95% CI = 1.03–1.50). In recent epidemiological studies the average risks reported were higher: with current usage of estrogen alone 1.18 (95% CI = 1.01–1.38) and with current usage of estrogen–progestin 1.70 (95% CI = 1.36–2.17). The suggestion of breast cancer with existing use was robust than the suggestion with ever use, which also includes past use. In case of past use, the amplified risk of breast cancer reduced soon after. Women who at an early age have their

first full term pregnancy are at low risk of developing breast cancer due to hormone receptor-positive breast cancer. Subsequently, late first pregnancy increases the risk of breast cancer (MacMahon *et al*, 1970). Another factor implicated in the development of breast cancer is obesity. It is believed that the high amount of adipose tissue results in elevated circulating levels of estrogen because in postmenopausal women estrogen is produced from the mediation of androgen by aromatase in the adipose tissue. Therefore, obese women appear to be exposed to increased estrogen level resulting in a heightened risk for breast cancer (Yasuo, 2005).

3.3. Breast Density

Breast density, which is a measure in the breast the level of radiodense fibroglandular tissue, was initially linked to heightened risk of breast cancer (Wolfe, 1976). It was established by quantitative analyses that women with high breast density were more likely by four to six times in developing breast cancer compared to women with breast tissue which is less dense (Kato *et al*, 1995; Boyd *et al*, 1995; Saftlas *et al*, 1991). Factors responsible for increased breast density include high exposure to estrogen and/or growth factors, elevated serum prolactin levels, and genetic factors (Harvey and Bovbjerg, 2004). In a recent meta-analysis it was noted a solid linear trend of growing risk of breast cancer with growing percentage of breast density (McCormack and Santos Silva, 2006). The mechanisms through which the risk of breast cancer through breast density are not entirely understood. Nevertheless, Boyd *et al*, (2005) studied that as the site of origin of breast cancers is the epithelial cell and breast density measures epithelial tissue in the breast, they suggested that higher breast density makes available a greater number of cells to a risk of uncontrolled proliferation.

3.4. Pre malignant lesions

A premalignant lesion which is a morphologically altered tissue is at a higher risk for malignant transformation than normal tissue. The best defined pre-malignant breast lesions comprise ADH (atypical ductal hyperplasia), ALH (atypical lobular hyperplasia), DIALH (with or without ductal involvement by cells of ALH), LCIS (lobular carcinoma in situ) and also in situ ductal carcinoma. Atypical ductal hyperplasia and unfolded lobules are occasionally considered as initial, pre-malignant lesions (Simpson *et al*, 2005; Lakhani *et al*, 1996; Boecker *et al*, 2001; O'Connell *et al*, 1998). Uncomplicated fibroadenomas, simple cysts, sclerosing adenosis, and stromal fibrosis are not linked with a clinically significant heightened breast cancer risk (Arpino *et al*, 2005). Studies have established that women who are

premenopausal and have been diagnosed with ALH are likely to develop bilateral breast cancer by four to five times (Page *et al*, 1985; Fitzgibbons *et al*, 1998; Collins *et al*, 2007; Dupont and Page, 1987). This is because premenopausal women are at a higher risk of breast cancer compared postmenopausal women with ALH (Collins *et al*, 2007; Page *et al*, 2003). It has been found that LCIS lesions are associated with double risk of breast cancer of ALH (Page *et al*, 1991; Fisher *et al*, 2004) Although it was initially believed that DIALH like LCIS increases the risk (Page *et al*, 1988), latest studies that involved a lengthier follow up period reported no statistically significant increased risk (Page *et al*, 2003). Atypical ductal hyperplasia has been linked to a somewhat lesser generalized increase in the risk of cancer than ALH, with a comparative risk of around three to four times that is observed in the general population (Fitzgibbons *et al*, 1998; Collins *et al*, 2007). DCIS which is a localized premalignant lesion is very likely to grow locally into invasive carcinoma if not excised (Mastracci *et al*, 2007).

3.5. Pathogenesis and classification of breast cancer

It is believed that breast carcinogenesis is a multi-step process (Dupont *et al*, 1993; Page *et al*, 1985). It has been proposed that breast cancer originates from benign breast lesions that may be with or without cellular atypia (ADH, ALH and atypical ductal hyperplasia) and develops into carcinoma in situ and ultimately into invasive carcinoma (Bodian *et al*, 1993; Carter *et al*, 1988; Dupont and Page, 1985). This hypothesis has been reinforced by molecular studies which demonstrated the changed expression of cell-cycle related and also seen in the premalignant lesions were apoptosis related proteins in invasive carcinoma (Mommers *et al*, 1998; Mommers *et al*, 2001). Correspondingly, identical genetic variations have been noted in premalignant lesions and invasive cancer (Simpson *et al*, 2005; O'Connell *et al*, 1998; Buerger *et al*, 2000; Nyante *et al*, 2004; Hwang *et al*, 2004). Studies have advocated that ADH, ALH usual ductal hyperplasia, and in situ disease could be precursors of carcinogenesis because they are more frequently found in breasts with invasive cancer (Bratthauer and Tavassoli, 2004, Alpers and Wellings, 1985). Epidemiological studies have confirmed that increasing morphological variations of breast lesions increase the risk of breast cancer (Dupont and Page, 1985; Wang *et al*, 2004; London *et al*, 1992; Dupont *et al*, 1993). These morphological variations occur slowly and progressively, providing a wide window of intervention.

Classification of breast cancers according to Devillee et al (2003):

- Non invasive (in situ)
 - Ductal carcinoma In situ
 - Lobular Carcinoma In Situ
 - Invasive Ductal Carcinoma

- Invasive
 - Invasive lobular carcinoma
 - Inflammatory breast cancer
 - Male breast cancer
 - Paget's disease of the nipple
 - Phyllodes tumors of the breast

3.6. Tumour markers

A substance present and/or overexpressed in or produced by the host (tumour-associated) or a tumour (tumour-derived), which can differentiate neoplastic from normal tissue, is defined as a tumour marker (Pamies and Crawford, 1996). Changes that occur within and on the surface of a cell during the alteration of a normal cell into a neoplastic cell can be used as a tumour marker. A tumour marker aids in detecting, staging and prognosis of cancer because it provides information about a cell at any given point (Zinnias *et al*, 2001). It also facilitates assessment of tumour burden, detection of recurrence, monitoring effects of therapy, screening of the general population and localization of tumours (Pamies and Crawford, 1996). A cost-effective method of observing cancer development has been found in tumour markers (Srivastava and Gopal-Srivastava, 2002).

In the following table, Table 1, tumour marker related research has been identified in association with breast cancer.

Table 1: Tumor markers identified in relation to breast cancer detection

Tumor markers	Author references
mucins, cancer antigen (CA) 15-3 and CA 27-29	Clinton et al, 2003; Safi et al, 1991, Frenette et al, 1994
oncofoetal protein and carcinoembryonic antigen (CEA)	Esteban et al, 1994; Sundblad et al, 1996
oncoproteins, homologue of epidermal growth factor receptor (HER2)	Imoto et al, 2007; Muller et al, 2006; Kong et al, 2006; Hudelist et al, 2006
c-myc	Breuer et al, 1994
p53	Balogh et al, 2006; Hassapoglidou et al, 1993
cytokeratins, tissue-type plasminogen activator (TPA)	Nicolini et al, 2006; Sliwowska et al 2006
ESR	Robertson et al, 1991 and 1999; Rubach et al, 1997
mammaglobin	Watson et al, 1996
survivin	Goksel et al, 2007 ; Yagihashi et al, 2005
livin	Yagihashi et al, 2005
NYESO- 1	Bandic et al, 2006
annexin XI-A	Fernández-Madrid et al, 2006
endostatin	Balasubramanian et al, 2007
Hsp90	Pick et al, 2007
p62	Rolland et al, 2007
koc	Zhang et al, 2003

For breast cancer, multiple serum-based tumour markers like CA 15-3, carcinoembryonic antigen (CEA)BR 27.29 (CA27.29), tissue polypeptide specific antigen, tissue polypeptide antigen, and HER-2 the extracellular domain have been defined (Duffy, 2006). None of the markers that are available are of value for the early detection of breast cancer because of a lack of specificity and a lack of sensitivity for early disease. For diagnosis preoperative concentrations of CA 15-3, CEA has been identified as high are identified as the most effective marker (Duffy, 2006) therefore we will do an in depth discussion of some of these markers. In patients with breast carcinoma elevated serum levels of CA 15-3 and CA 27.29 have been reported (Bastet al, 2001, Rodriguez de Paternaet al, 1995). With a specificity of around 87% and aa sensitivity of nearly 57%, recurrent breast carcinoma can be detected by

CA 27.29. (Rodriguez de Paterna *et al*, 1995). Similarly, 70% of cases of recurrent cancer reported and raised serum levels of CA 15-3 (Bast *et al*, 2001). CEA, which is a cell surface glycoprotein, is a marker for gastrointestinal, lung, colorectal, and breast carcinomas. Though raised serum levels of CEA do not draw a parallel to tumour grades in breast cancer, they are still used to detect recurrence and monitor therapy (Bates and Longo, 1987). Aggressive growth and poor diagnosis in ovarian and breast cancer have been associated with elevated levels of HER-2 (Slamon *et al*, 1989; Tiwari *et al*, 1992). In over 50% of the tumours, p53 which is a tumour suppressor gene is mutated. Guillot *et al* (1996) confirmed the association of p53 with tamoxifen resistance in breast cancer, which in turn suggests that it interferes with treatment response.

3.7. Prognostic and predictive factors

A measurable variable that draws a parallel with the natural history of the disease may be defined as a prognostic factor. It can also be used to define the recurrence of the disease and the probability of recovery (Cianfrocca and Goldstein, 2004). Predictive factors that could be possibly defined as measurable variables are related with response to any given therapy (Cianfrocca and Goldstein, 2004). Some factors can be both predictive and prognostic.

Estrogen and Progesterone receptors

It is both predictive and prognostic that progesterone and estrogen receptors are present in invasive breast carcinoma. A random trial verified that in 74% of women with -positive tumours estrogen receptors (ER) had a 5 year DFS (disease free survival) and 92% had OS (overall survival) in comparison 66% of women had a 5 year DFS and 82% OS in women who had ER-negative tumours (Fisher *et al*, 1988). Nevertheless, Hilsenbecker *et al* (1998) observed improved diagnosis for ER+ tumours within the first 3 years that could not have sustained after 3 years.

It has been determined that the presence of progesterone or estrogen receptors is prognostic of chance of improvement from adjuvant tamoxifen and Annexin 1 (A1) in first degree tumour. A randomized control trial established that using adjuvant tamoxifen for 5 years reduces the risk of mortality and recurrence in patients with tumours that are ER-positive to 47% and 26% respectively. The outcome was reduction of absolute mortality in patients with lymph node-negative disease by 5.6% and in patients with node-positive disease by 10.9%. Contralateral breast cancer risk was reduced by 47% by five years of

adjuvant tamoxifen. However, in patients with ER-negative tumours these benefits of tamoxifen were not detected (Early Breast Cancer Trialists' Collaborative Group, 1998). Another potential marker for the development of breast cancer is Annexin A1 (ANXA1). A conceivable part for ANXA1 in the initial events of malignant alteration may be suggested by the absence of ANXA1 expression in the bulk of breast carcinomas and in in situ carcinoma the primary loss of ANXA1 expression, that is maintained in both metastatic and invasive tumours, (Cao et al., 2008).

HER2/neu -Human Epidermal Growth Factor Receptor 2

The proto-oncogene *HER2/neu*(c-erbB-2) encodes a transmembrane glycoprotein that has an inherent tyrosine kinase activity which is homologous to the epidermal growth factor receptor (Schechter et al, 1984). It is overexpressed and/or amplified in approximately 30% of human breast cancers (Slamon et al, 1987). Overexpression is linked to increase in tumour aggressiveness, amplified rates of recurrence and heightened mortality in node positive patients, whereas in node negative patients its influence is variable (Borg et al, 1990; Winstanley et al, 1991; Paterson et al, 1991; Clark and McGuire, 1991).

It has been proposed that the overexpression of *HER2/neu* plays a prognostic role in response to endocrine and chemotherapy therapy. Though when administered 5-flourouracil (CAF) or adjuvant anthracycline, cyclophosphamide, or adriamycin, an enhanced treatment result has been observed in women who are *HER2/neu* positive (Ravdin et al, 1998; Vera et al, 1999; Paik et al, 1998; Pritchard et al, 2002), its overexpression of *HER2/neu* has been associated with resistance to alkylator-based chemotherapy (Gusterson et al, 1992; Allred et al, 1992). *HER2/neu* overexpression can be used in identifying patients who have a chance of benefitting from advanced doses of adjuvant chemotherapy (Muss et al, 1994). However, it is still unclear what influence *HER2/neu* response has on the endocrine therapy (Carlomagno et al, 1996; Blanco et al, 1998; Constantino et al, 1994; Ellis et al, 2001). *HER2/neu* status has also been observed to predict specific response to a *HER2* antibody, for instance: trastuzumab in a metastatic setting (Baselga et al, 1996; Cobleigh et al, 1998).

Urokinase-Type Plasminogen Activator (uPA) and Plasminogen Activator Inhibitor type 1 (PAI-1)

It has been established that uPA and PAI-1 have predictive and prognostic value. Node negative patients who report low uPA/PAI-1 have shown exceptional prognosis with 5 year

DFS over 90%, without systemic adjuvant therapy, whereas node negative patients who reported high uPA/PAI-1 show a heightened risk of relapse (Janicke *et al*, 2001; Harbeck *et al*, 1999; Harbeck *et al*, 2002). Primary breast cancer patients, patients whose cancer hasn't spread beyond the breast (Henderson *et al.*, 2003), with high uPA and PAI-1 demonstrated an enhanced response to adjuvant chemotherapy as compared to those who had low levels (Harbeck and coworkers 2002).

Genetic profiling

Predictive and prognostic information on breast cancer can be provided by gene expression profiles available from microarray analyses. Van de Vijver *et al* (2002) made the use of oligonucleotide microarrays to acquire gene-expression signatures, which aided them in classifying the prognosis of patients with stage I or stage II breast cancer. Out of the 295 patients, 115 had a good-prognosis signature and 180 had a poor-prognosis signature, and also the average (+/-SE) complete 10-year survival rates were 94.5+/-2.6 percent and 54.6+/-4.4 percent respectively. At 10 years, the likelihood of enduring free of distant metastases in the group with a good-prognosis signature was 85.2+/-4.3 percent and in the group with a poor-prognosis signature was 50.6+/-4.5 percent. The projected risk ratio for distant metastases in the group that had a poor-prognosis signature, in comparison to the group that had the good-prognosis signature, was 5.1. The follow up lasting 10 years showed that OS and DFS and rates were 54.6% and 50.6%.

EXPRESS DISSERTATION