# THE ASSOCIATION BETWEEN DEMOGRAPHY, ANTHROPOMETRY, SERUM ESTROGEN AND BREAST DENSITY IN PATIENTS HAVING MAMMOGRAPHY IN HOSPITAL UNIVERSITI SAINS MALAYSIA

By

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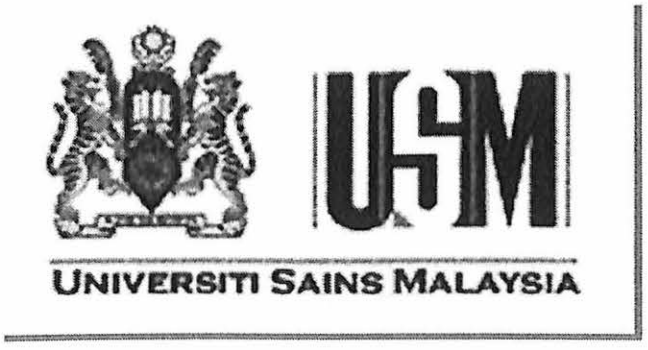
**Dissertation Submitted In Partial Fulfillment Of The Requirements For The Degree Of Master Of Medicine (Radiology)**

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To

My beloved husband

A strong determinant person

His loves, patience, understanding and moral support enables me to complete this project and my master program.

My two lovely sons

Muhamad Afif and Muhamad Iman

Their cheers and smiles relief my stress

Their understanding make all this possible

My in-laws

Thanks for their full moral support

They enlighten my day and my daily duties

My mother

Her loves and constant moral support make me

a better and stronger person

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# ABBREVIATIONS

| | |
|---|---|
| ANCOVA | Analysis of covariance |
| BIRADS | Breast Imaging And Data System |
| BMI | Body mass index |
| CC | Cranio-caudal |
| HUSM | Hospital Universiti Sains Malaysia |
| HRT | Hormone Replacement Therapy |
| MLO | Mediolateral oblique |
| MRI | Magnetic Resonance Imaging |
| SPSS | Statistical Software for Social Sciences |
| WHR | Waist hip ratio |

# ABSTRAK

**Topik**: Perkaitan Antara Demografi, Antropometri, Serum Estrogen dan Ketebalan Tisu Payudara Di Kalangan Pesakit Yang Membuat Pemeriksaan Mamografi di Hospital Universiti Sains Malaysia.

**Latarbelakang:** Kanser payudara merupakan kanser yang biasa di kalangan wanita. Mengikut laporan dari Malaysia National Cancer Registry 2002, kanser payudara menyumbangkan lebih kurang 30.4% dari keseluruhan kes-kes kanser diikuti oleh kanser serviks (12.4%). Banyak faktor telah dikenalpasti sebagai penyumbang kepada peningkatan risiko kanser payudara ini. Salah satu daripadanya ialah ketebalan tisu payudara. Tisu payudara yang tebal dalam pemeriksaan mamografi juga dikatakan berkaitan dengan proliferasi epitelium and parut stroma. Kaitan antara jenis histologi tisu payudara dan risiko kanser boleh diterangkan melalui tindakan faktor pertumbuhan (hormon) yang memainkan peranan dalam perkembangan fisiologi payudara dan proses pertumbuhan kanser. Risiko ini juga mungkin disebabkan tisu payudara yang tebal menghalang kanser daripada mudah dikesan. Faktor-faktor lain seperti wanita yang tidak pernah mengandung (nulipariti), mengandung sulung pada lewat umur, umur lebih muda, bilangan anak, umur dan jangkamasa putus haid, indeks jisim badan, pengambilan hormon gantian dan serum estrogen berkemungkinan menyebabkan risiko kanser payudara melalui kesan tidak langsung terhadap ketebalan tisu payudara. Oleh itu kajian ini bertujuan mengkaji sama ada wujud perkaitan antara faktor demografi, antropometri, serum estrogen dan ketebalan tisu payudara.

**Metodologi dan Bahan**: Ini merupakan kajian keratan lintang selama 1 tahun bermula dari bulan Mei 2004 sehingga Mei 2005. Data diambil dari pesakit yang datang untuk melakukan pemeriksaan mamografi di Jabatan Radiologi, Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan di dalam tempoh tersebut. Data daripada 84 orang pesakit berjaya dikumpulkan.

**Keputusan:** Terdapat perkaitan yang ketara antara indeks jisim badan (p=0.033), bilangan anak (p=0.002) dengan ketebalan tisu payudara. Indeks jisim badan mempunyai perkaitan songsang dengan ketebalan tisu payudara. Keputusan menunjukkan bahawa pesakit yang mempunyai indeks jisim badan yang tinggi mempunyai kebarangkalian lebih rendah untuk berkait dengan tisu payudara yang tebal. Setiap satu unit kenaikan indeks jisim badan, kebarangkalian untuk berkait dengan tisu payudara yang tebal adalah 0.86 kali. Bilangan kelahiran juga berkadar songsang dengan ketebalan tisu payudara. Bagi setiap pertambahan bilangan kelahiran, kemungkinan untuk mempunyai tisu payudara yang tebal menurun sebanyak 31% (95% CI, penurunan risiko dari 12% hingga 46%). Serum estrogen walau bagaimanapun bukan merupakan variabel tersendiri yang ketara terhadap tisu payudara.

**Kesimpulan:** Indeks jisim badan dan bilangan anak tetapi tidak serum estrogen mempunyai perkaitan ketara dengan ketebalan tisu payudara setelah mengambil kira faktor luaran yang boleh mempengaruhinya.

# ABSTRACT

**Topic**: The Association between Demography, Anthropometry, Serum Estrogen and Breast Density in Patients Having Mammography in Hospital Universiti Sains Malaysia

**Background:** Breast cancer is the most common cancer in female. Report from Malaysia National Cancer Registry (NCR) 2002 showed that breast cancer account for 30.4% of all cancers followed by cervical cancer (12.4%). Many contributing factors have been identified to increase the risk of developing breast cancer. One of the factors is breast density. Dense breast tissue by mammography is associated both with epithelial proliferation and with stromal fibrosis. The relationship between these histological features and risk of breast cancer may be explained by the known actions of growth factors (hormones) that are thought to play important roles in breast development and carcinogenesis. The risk might be partly due to masking of tumors by dense tissue. Other factors such as nulliparity, late age at first birth, younger age, parity, age and duration of menopause, body mass index, hormone replacement therapy and serum estrogen may potentially affect breast cancer risk through their indirect effect on breast density. The aims of the study were to determine the characteristics of patients with mammography in Hospital Universiti Sains Malaysia and to determine the independent variables associated with breast density.

**Methods and Materials:** This study was a cross-sectional study conducted for one year duration from May 2004 to May 2005. Data were taken from patients who came for

mammography in Radiology Department, Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan during the study period. Data from 84 patients were collected.

**Results:** Significant association noted between body mass index (p=0.033), parity (p=0.002) and breast density. Body mass index showed inverse relationship with breast density meaning that patients with higher body mass index had lower chance of being associated with dense breast. Results showed that for every one unit increase in body mass index, there is 0.86 times chance of association with dense breast. Inverse relationship also noted between parity and breast density. One unit increased in parity was associated with 31% reduction in chances of having dense breast (95% CI, risk reduction range from 12% to 46%). Serum estrogen however was not a significant independent variable for breast density.

**Conclusion:** Body mass index and parity but not serum estrogens were significantly associated with breast parenchyma when adjusted for potential confounding factors.

# SECTION 1

# INTRODUCTION

# 1 INTRODUCTION

## 1.1 Epidemiology

It is depressing to see the current global health trend as the incidence of cancer among population is on the rise. Many factors have been identified as contributing factors to these phenomena. These could be due to our environment and lifestyle. Based on the report from the Malaysia National Cancer Registry (NCR) 2002, the cumulative risk of cancer in Peninsular Malaysia was 18% meaning that 1 in 5.5 Malaysians can be expected to get cancer in their lifetime. Taking into account cancer cases which were not registered by the NCR, the risk could be higher with probably 1 in 4 Malaysians getting cancer in their lifetime (Ministry of Health Malaysia 2002). It was also reported that the incidence is higher in Chinese and Indians compared to Malays. The different in racial incidence is most likely due to contributing risk factors such as lifestyle. The Chinese have a higher status of socioeconomic, more likely to have less children, have their children later in life and less likely to breast feed their children than Malays. Other factors could be due to dietary intake and genetic predisposition among races. However, there is lack of data on genetic predisposition among races in Malaysia (Har 2005).

Second Report from the Malaysia National Cancer Registry (NCR) 2003 reported crude rate of cancer incidence for males was 97.4 per 100,000 population and 127.6 per 100,000 populations for female. Median age at diagnosis for males was 59 and for females were rather younger, 53. The common cancers among females were breast, cervix, ovary, uterus, thyroid gland and leukemia. Among females, the most frequent cancer was cancer of the breast (31.0% of all female cancer) which is significantly higher than the second most common cancer that is cervical cancer

(12.9%). In regards to female breast cancer, in 2003 there were 3738 cases reported accounted for 31.0% of newly diagnosed female cases. It was the commonest cancer in all ethnic groups and all age groups from the age of 15. Peak age incidence was 50-59 and 64.1% were women between 40 and 60 years of age (Ministry of Health Malaysia 2003).

In view of the above mentioned scenario, we can make a conclusion that in overall, cancer (breast cancer especially) is a serious health problem without overlooking on other major health problems such as cardiovascular disease, diabetes mellitus, hypertension etc.

## 1.2 Breast density and breast cancer

Breast density is an important contributing factor for breast cancer and the influence of breast density on the risk of developing breast cancer has been discussed in many studies and published in many articles. Many studies have been done to look for association between breast density and risk factors for breast cancer. Few studies emphasized on factors affecting breast density such as body mass index, smoking, nulliparity, hormone replacement therapy, age at menarche, menopausal status, race, diet and family history of breast cancer.

A large study was conducted to assess the role of the Wolfe classification of breast parenchyma pattern as a breast cancer risk together with a set of well-established risk factors for breast cancer. The study showed that there was an

association between parenchyma pattern and the risk of breast cancer (Carlile, J.Kopecky et al. 1985).

Study done by Van Gils on relationship between parity and breast cancer risk showed 7.1 increased risk of breast cancer in nulliparous women with breast density of ≥5%. The result of the study suggested that high breast density (reflecting fibro-glandular tissue with increased epithelial cell proliferation) was more susceptible to carcinogenic effects (Van Gils 1999).

Recent epidemiological studies have reported more than four-fold higher risk of breast cancer for higher breast density. This is biologically explained as breast cancers arising from the epithelial lining of the ductal glandular structures (Van Gils 1999). Egan and Mosteller hypothesized that the association between breast density and subsequent risk of cancer might be due to "masking" of tumour by dense tissue (Benichou, Byrne et al. 2003). This could be due to reduction in sensitivity of mammogram in dense breast.

Study also has been done to look for association between age, menopausal status and breast cancer risk. Byrne et al. found a greater effect of breast density on risk of breast cancer in post menopausal women compared to pre menopausal women. Another study by Boyd et al. also found higher risk for women age 50-59 compared with women age 40-49. However, because of small sample size, these two studies did not show strong relationship between increased breast density and cancer risk according to menopausal status (Harvey and Bovbjerg 2004).

Understanding the physiological changes of breast parenchyma throughout life is crucial in order to know the confounding factors affecting breast density. It is well explained by many literatures that the density of breast tissue is influenced by the hormonal status particularly the estrogen level. Physiological changes of breast parenchyma have been discussed in detail in the Literature Review (Section 2). However, it is still a controversial issue whether breast density is an independent risk factor or plays a role as a marker for breast cancer.

## 1.3 Breast Awareness Program

There are many campaigns and programs launched by the Ministry of Health Malaysia to either reduce the incidence of major health problems in general or cancers especially breast cancer. One of the programs is breast screening program in which it encourages women at the age of 40 and above to have their breast screened for malignancy. Self breast examination has also been promoted as a method to detect any breast abnormality.

Guidelines for mammography for Breast Screening in Malaysia have been outlined by the General Practice Guideline. The guidelines include high risk women with past history of breast and or ovarian cancer, family history of breast cancer in one or more first or second degree relatives before the age of 50 years and history of cellular atypia on previous biopsy before the age of 40 years and asymptomatic women. Mammography should be done annually for women age 40-49 years and annually or biennially for women age 50-75 years old (Ministry of Health 2002).

Mammography is the best method to screen for any breast lesions. However, there is 20% false negative rate of mammography. Therefore, correlation between mammography and clinical findings are very important. A recent report from National Evaluation Team for Breast Cancer Screening (NETB) indicated cancer detection rates of 4.5-10 per 1,000 for prevalence screens and 3.0-4.8 for incidence screens. The positive predictive value of an abnormal mammogram was 50-60%.

## 1.4 Breast cancer risks

Several factors have been identified as potentially responsible for increasing breast cancer risk. These factors are:-

i) Previous history of breast cancer.

ii) Increasing age.

iii) Geographic variation.

iv) Family history.

v) Biopsy confirmed benign proliferative breast disease

i) Previous radiation to the breast.

ii) Nulliparity (women who never been pregnant) at 40 years of age.

iii) First full term pregnancy at age of 35 or more.

iv) Early menarche (aged 12 and younger).

v) Late menopause (age 55 and older).

vi) History of primary cancer of the ovary or endometrial.

vii) Obesity in postmenopausal women.

viii) Evidence of specific genetic susceptibility (such as carriage of BRCA1, BRCA@ or BRCA3).

ix) Staple diet containing red meat, high total fat (especially saturated fat) and alcohol.

x) Hormone replacement therapy – the Women Health Initiative study found an increased risk of breast cancer (Hazard Ratio 1.26) in women on hormone replacement therapy with combined estrogen plus progestin given in a continuous manner.

The above mentioned factors are directly contributing to the risk of breast cancer through direct pathological influence. As there are many potential causes contributing to breast cancer, many studies and effort have been put up to either reduce the risk of breast cancer or detect the problem early. Many studies have been done to look for association between the risk factors and occurrence of breast cancer. Based on these studies, many theories and hypothesis have been postulated and published and opened for discussion.

Women with previous history of breast cancer have 5-fold increased risk of breast cancer in the contra-lateral breast. The risk is about 1% per year of survival and increased in the presence of other associated risk factors such as hereditary breast cancer and proliferative changes in the remaining breast (Sakorafas 2002).

Prospective cohort study for 18 years in 6689 women participating in the Copenhagen City heart study concluded that high endogenous concentrations of estrogen are a known risk factor for breast cancer and impairment of estrogen synthesis induced by chronic stress may explain a lower incidence of breast cancer in women with high stress. However, this is not considered a healthy response, and the

cumulative health consequences of stress may be disadvantageous (Nielsen, Zhang et al. 2005).

Obesity is a known factor for breast cancer. Harvey and Bovberg 2004 in their article wrote that Lam et al. examined the relationship between the weight and body mass index on the association of breast density and breast cancer risk. It was found that women with higher body weight and body mass index were less likely to have dense breast. However, after adjusted for weight and body mass index, the odd ratio was increased to 4.5. The study concluded that the confounding of these two factors on breast cancer risk tends to be underestimated when not adjusted for body mass index (Harvey and Bovbjerg 2004).

Mutation in BRCA gene is a known genetic susceptibility factor for breast cancer. The risk is different between the non-Ashkenazi Jewish or Ashkenazi Jewish. For non-Ashkenazi Jewish those at risk are, any 2 first-degree relatives with breast cancer, 1 of whom received the diagnosis at the age of 50 years or younger; a combination of 3 or more first-degree or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancer among first-degree and second-degree relatives; a first-degree relative with bilateral breast cancer; a combination of 2 or more first-degree or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first-degree or second-degree relative with both breast and ovarian cancer at any age; and a history of breast cancer in a male relative. For women of Ashkenazi Jewish heritage, an increased-risk family history includes any first-degree relative (or 2 second-degree relatives on the same side of the family) with breast or ovarian cancer (U.S Preventive Task Force 2005).

Study on mutation spectrum of BRCA1 gene done on 49 Malay breast cancer patients in Singapore strongly suggest that the 2845insA mutation, the most common deleterious mutation in the study may possibly a founder mutation in breast cancer patients of Malay ethnic background (Lee, Ho et al. 2003).

Knowing the above mentioned facts, this study was designed to look for any association between the risk factors for breast cancer such as estrogen level, demographic characteristic, anthropometric measurement and breast density. Consideration was also given for other factors such as age, menstrual history, menopausal status, body mass index, waist hip ratio and reproductive factors such as parity. This study was designed to look for any significant association between the above factors and to discuss on the possible explanation regarding association. As most of the studies were done by the Western Countries, probably the author would like to know the data for the Malaysian population or specifically for the patient who came for mammography in Hospital Universiti Sains Malaysia. Many studies have been done by the Western countries on factors associated with breast density but no similar study has been done locally. Results from this study might be useful in preventive management of breast cancer in Malaysia.

# SECTION 2

# LITERATURE REVIEW

# 2 LITERATURE REVIEW

## 2.1 Anatomy of the breast

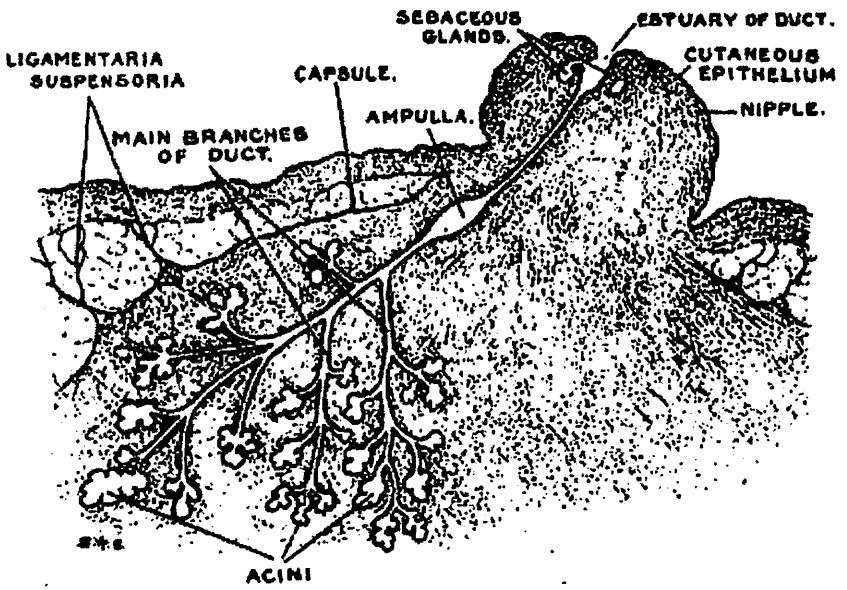


**Figure 2-1 Breast ducts, lobules and terminal acini**

(G. Grainger and Allison 1999)

The breast contains 15–20 lobes. Each lobe comprises a variable number of lobules, which consist of 10–100 acini or blind-ending sacs (Figure 2-1) (G.Grainger and Allison 1999). Fifteen to twenty lobes disposed radially around nipple and each lobe has a main lactiferous duct of 2.0-4.5mm converging at the nipple with an opening in the central portion of the nipple (Dahnert 1996).

The breast ducts form a branching structure that conveys milk from the acini to the nipple. The various sized ducts can be described on the basis of their location as intralobular, interlobular, intralobar and interlobar (G.Grainger and Allison 1999).

### 2.1.1 Surface anatomy of the female breast

The adult female breast lies vertically from the 2nd to the 6th rib and in the transverse plane from the lateral border of the sternum to the mid-axillary line.

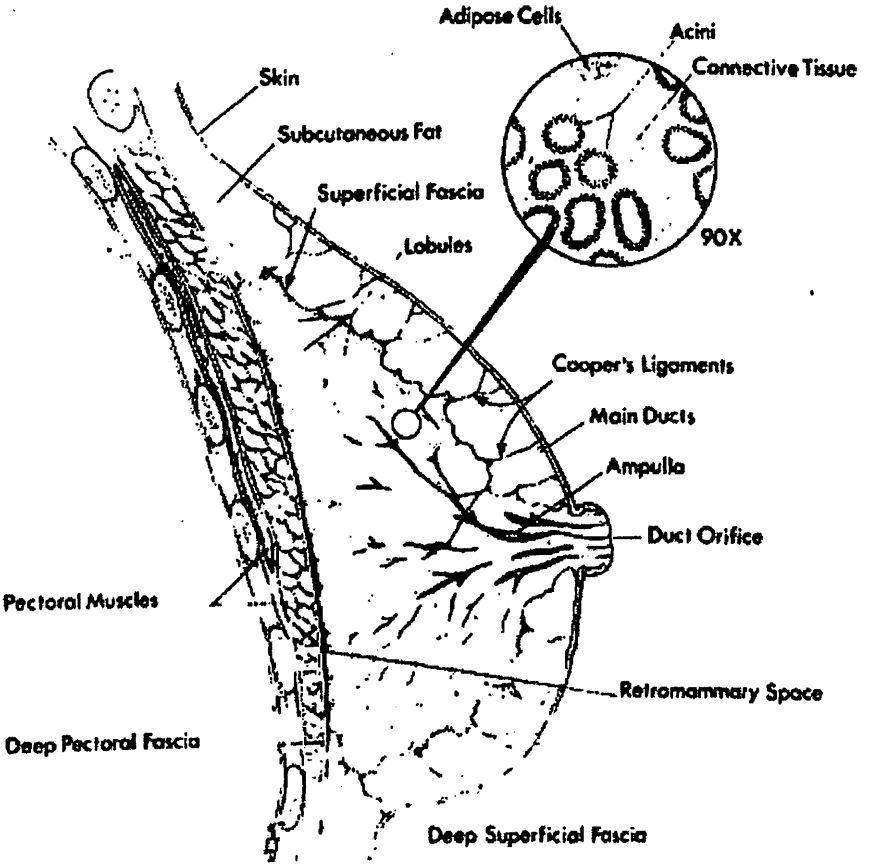


**Figure 2-2 Surface anatomy of the breast**

(G.Grainger and Allison 1999)

Breast is made up of essentially three distinct components. Glandular and ductal tissue constitutes the parenchyma. These tissues are the most important component and they are arranged in lobes. Between the glandular tissues run fibrous and fatty tissues. No distinct capsules seen but the subcutaneous tissue which envelop the gland send septa into it to act as a supporting framework for the various lobules. The fibrous tissue at it most developed upper part of the breast is known as suspensory ligaments (Tucker and Ng 2001).

### 2.1.2 Blood supply

The arterial supply to the breast is from the lateral mammary branch of the lateral thoracic artery, the anterior cutaneous perforating branch of the internal mammary artery and branches are also derived from the $2^{nd}$ to the fifth intercostals arteries.

The veins describe an anastomotic circle around the base of the nipple, so called the circulus venosus which then drains into axillary and internal mammary veins (Tucker and Ng 2001).

### 2.1.3 Lymphatic drainage

It is divided into superficial and deep plexus of lymphatic vessels. The superficial plexus lies beneath the skin superficial to the gland. The deep plexus lies in deep fascia of which the mammary gland rests. The lymphatic drainage is as

illustrate in the diagram. This lymphatic drainage is very important in understanding the spread of malignant disease (Tucker and Ng 2001).

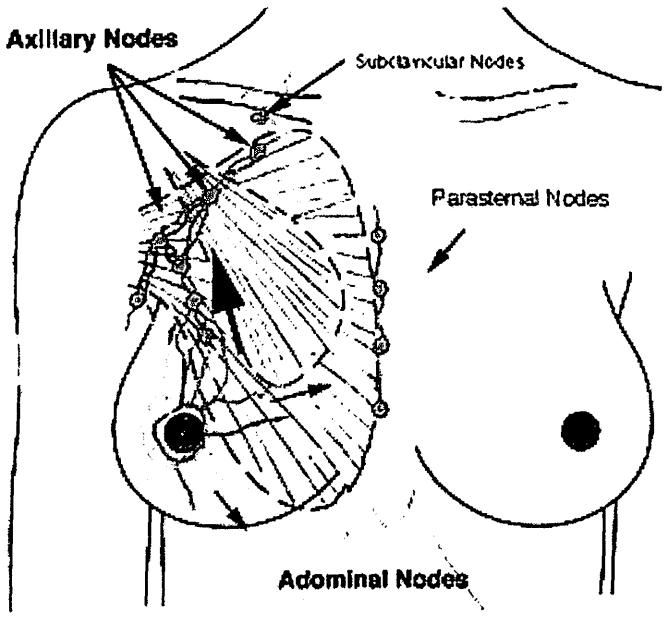


**Figure 2-3 Lymphatic drainage of the breast**

Adapted from the Internet (Anonymous)

### 2.1.4 Nervous supply

Breast is supplied by the lateral and anterior cutaneous branch from the 4$^{th}$, 5$^{th}$ and 6$^{th}$ intercostals nerves (Tucker and Ng 2001).

## 2.2 Physiological changes of the breast

Female breasts do not begin growing until puberty that is the period in life when the body undergoes a variety of changes to prepare for reproduction. Puberty usually begins for women around age 10 or 11. After pubic hair begins to grow, the breasts

will begin responding to hormonal changes in the body. Specifically, the production of two hormones, estrogen and progesterone, signal the development of the glandular breast tissue.

The size and shape of women's breasts varies considerably. Some women have a large amount of breast tissue, and therefore, have large breasts. Other women have a smaller amount of tissue with little breast fat.

Factors that may influence a woman's breast size include volume of breast tissue, family history, age, weight loss or gain, history of pregnancies and lactation, thickness and elasticity of the breast skin, degree of hormonal influences on the breast (particularly estrogen and progesterone) and menopause.

Breast shape and appearance undergo a number of changes as a woman ages. In young women, the breast skin stretches and expands as the breasts grow, creating a rounded appearance. Young women tend to have denser breasts (more glandular tissue) than older women.

The mature breast undergoes cyclic changes during the menstrual cycle. Estrogen increases cell proliferation and progesterone enhances this effect. During the follicular phase, cell proliferation increases and is further enhanced during the luteal phase. During each menstrual cycle, breast tissue tends to swell from changes in the body's levels of estrogen and progesterone. The milk glands and ducts enlarge, and in turn, the breasts retain water. During menstruation, breasts may temporarily feel swollen, painful, tender, or lumpy.

### 2.2.1 Breast changes during pregnancy

During pregnancy, a variety of breast changes occur. Typically, breasts become tender and the nipples become sore a few weeks after conception. The breasts also increase in size very quickly. It is not uncommon for a woman's breasts to increase by one or two cup sizes during and after pregnancy. The most rapid period of breast growth is during the first eight weeks of pregnancy. The Montgomery's gland surrounding the areola (pigmented region surrounding the nipple) becomes darker and more prominent, and the areola itself darkens. The nipples also become larger and more erect as they prepare for milk production. The blood vessels within the breast enlarge as surges of estrogen stimulate the growth of the ducts and surges of progesterone cause the glandular tissue to expand.

### 2.2.2 Breast changes after menopause

After the menopause, the mammary gland tissues atrophies or involutes. Ovarian hormones are no longer stimulated and the secretory cells of the alveoli degenerate. Some of the ductal tissues remain and the connective tissue components are also degenerate.

## 2.3 Physiology of reproductive hormones

Understanding the physiology of the reproductive system is useful in determining the hormonal level and reproductive status of women. Women who are still menstruating are considered to be fertile. This fertile period starts at menarche and ends with the menopause

### 2.3.1 Menstrual cycle

Menstrual cycle starts at the first day of menses and ends at the day preceding the next menstruation. This period is divided in cycle of 28 to 35 days in length separated by menstruation.

### 2.3.2 Hormones of the menstruation

The regulation of hormones is through the hypothalamic-pituitary axis. Gonadotrophin Releasing Hormone (GnRH) controls the release and synthesis of Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH).

The action of FSH is to allow recruitment and growth of the ovarian follicles while LH induces follicular rupture and sustain the corpus luteum. Estradiol is produced by the follicles and Progesterone by the corpus luteum (Bischof 2003).

### 2.3.3 The endocrine and physiology of menstrual cycle

The interplay between pituitary and ovarian hormones gives rise to a stereotyped pattern of hormone level during the menstrual cycle. The graph below shows relative hormone levels in an average 28-day cycle.

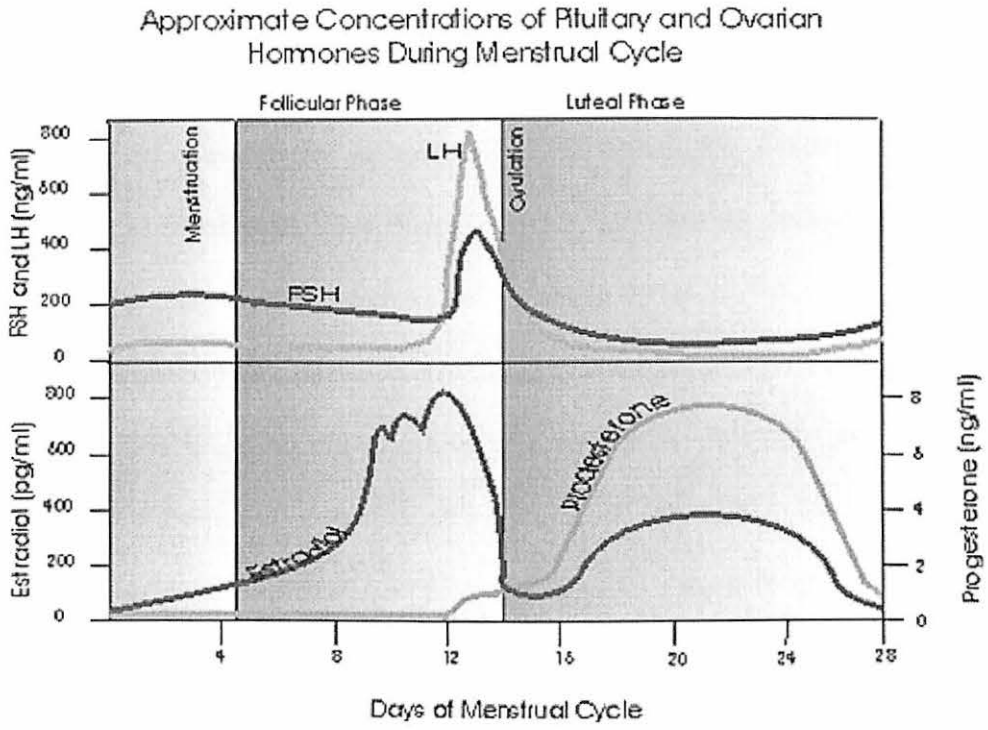


**Figure 2-4 Approximate concentrations of pituitary and ovarian hormones during menstrual cycle**

Adapted from Internet (Anonymous)

Figure 2-4 represent the variation in serum estradiol level during menstruation. The serum estradiol started to surge after the starting of menstruation and continues to increase during the Follicular Phase until the starting of ovulation. After the ovulation that is during the Luteal Phase, there is period when the estradiol level is at the stable level. This is at about day 16 to 24 of menstrual cycle.

## 2.4 Breast density assessment

There are many ways to assess the mammography density of the breast parenchyma. More accurate assessment of breast density is by measuring the amount of breast tissue by digital mammography using the available software. Another method of assessing the breast density is by qualitative assessment through breast parenchyma pattern. Even though qualitative assessment of breast density is not as accurate as computer-aided measurement, crudely we are able to use the parenchyma pattern to categorize the breast into the dense and the non-dense type of breast tissue. Breast parenchyma pattern as describe in Literature Review (page 18-23) is a method of describing the amount of fat and glandular tissue in the breast. Dense breast will have more amount of glandular tissue compared to the non-dense breast which has more amount of fat.

Study by Van Gils et al measured the breast density by measuring the breast tissue from a digitized mammogram. The study categorized into the breast density into < 5%, 5-25% or > 25% density (Van Gils 1999). Semi-quantitative assessment of breast density by Boyd classification scale was used in study on breast density and breast cancer risk factors in a high risk population (Warwick, Pinney et al. 2003). Four categories of breast parenchyma as described by Wolf was N1, P1, P2 and DY (refer to page 18-23 on Literature Review). BIRADS also described four categories of breast parenchyma similar to Wolfe (Vacek and Geller 2004). Another study categorized breast parenchyma density into less than 25%, 25-49.99%, 50-69.99% and 70-99.99%. The <25% and 25-49.99% groups were grouped into corresponding N1 and P1 pattern which is taken as reference category and the rest two groups were put into corresponding P2 and DY pattern as described by Wolfe which is taken as high risk group for breast cancer (Wolfe, Saftlas et al. 1987). In our study, BIRADS

classification of breast parenchyma pattern was used as reference of mammography parenchyma breast densities as it is readily used by the Radiologists in our department in assessing large number of mammograms.

The classification of breast parenchyma patterns is based on relative amount of radiographic densities that corresponds to connective and epithelial tissues within the breast (Wolfe, Saftlas et al. 1987). There are many mammographic classification of the breast parenchyma pattern which represents the breast density. The density of the breast parenchyma can be assessed qualitatively or quantitatively. Qualitatively the breast parenchyma is classified using Wolfe, Laszlo Tabar and BIRADS (American College of Radiology Breast Imaging and Data System) methods. Semi quantitative assessment was done by Boyd et al. and quantitative measurement was made by computed-aided calculation of fibro-glandular area from digitized mammograms. (Chow, Venson et al. 2000)

### 2.4.1 Wolfe classification

Wolfe method described four parenchyma patterns based on the relative amount of fat, epithelial and connective tissue density

N1: normal. The breast parenchyma is of low density and has a large proportion of fat. No ducts are visible.

P1: the parenchyma is composed mainly of fat, with a prominent duct pattern in the anterior portion of the breast but involving less than one quarter of the breast volume.

P2: prominent duct pattern which involves more than one-quarter of the breast volume and often associated with nodular component.

DY: increased density of the breast parenchyma with or without areas of nodularity. The density often obscures the underlying duct pattern. (Tucker and Ng 2001).

### 2.4.2 Laszlo Tabar classification

Laszlo Tabar classification is slightly different from Wolfe as presence of additional pattern and more detail description of each pattern.

Pattern I: concave contour from Cooper's ligaments with evenly scattered 1-2mm nodular densities and oval-shaped/circular lucent areas.

Pattern II: total fatty replacement without nodular densities. Has similar description with N1 pattern by Wolfe.

Pattern III: normal parenchyma occupying <25% of breast volume in retro-areola region. It is similar to P1 (Wolfe).

Pattern IV: also called adenosis pattern. Described as scattered 3-7mm nodular densities (enlarged terminal ductal lobular unit), thick linear densities (periductal elastic tissue proliferation with fibrosis). This type of parenchyma pattern is genetically determined and does not change with increasing age. It is similar to P2 (Wolfe).

Pattern V: uniformly dense parenchyma with smooth contour (extensive fibrosis). It is similar to DY (Wolfe) (Dahnert 1996).

### 2.4.3 BIRADS classification

BIRADS method classifies breast parenchyma into four categories:-

(I) Fatty

(II) Scattered fibro-glandular densities

(III) Heterogeneously dense

(IV) Extremely dense

**Figure 2-5 Fatty breast**

Adapted from Internet (Interactive Mammography Analysis Web Tutorial)

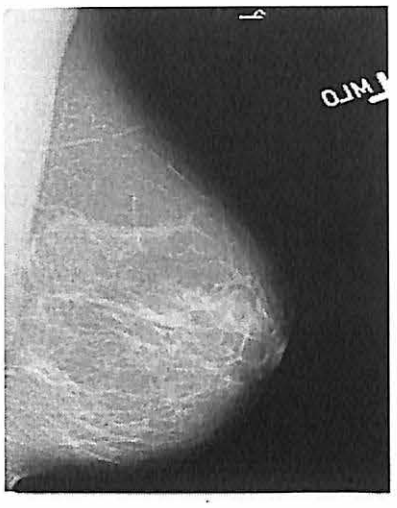

**Figure 2-6 Scattered fibro glandular density**

Adapted from Internet (Interactive Mammography Analysis Web Tutorial)

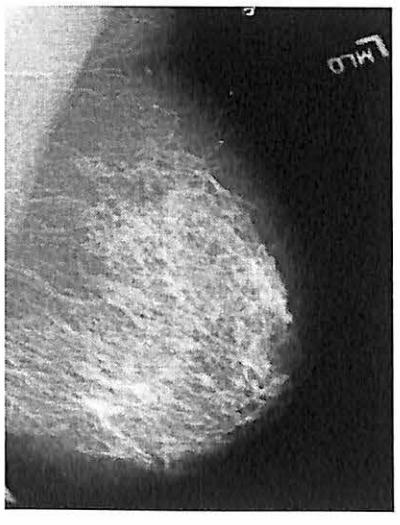

**Figure 2-7 Heterogeneously dense**

Adapted from Internet (Interactive Mammography Analysis Web Tutorial)


**Figure 2-8 Extremely dense**

Adapted from Internet (Interactive Mammography Analysis Web Tutorial)

### 2.4.4 Boyd classification

Semi quantitative assessment by Boyd et al. classified breast parenchyma into six categories:-

(a) Density = 0%

(b) Density = >0% to <10% of the area of breast

(c) Density = 10% to <25%

(d) Density = 25% to <50%

(e) Density = 50% to <75%

(f) Density = >75%

### 2.4.5 Computer-aided quantitative assessment

For computer-aided quantitative assessment, the films were digitized using Dicomed digital camera at 267dots/inch. These data is saved as TIFF files. The analysis of the digitized films was performed on a Power Macintosh 6100/66 computer using the NIH Image program. The region of interest is then manually outlined and the region of interest is interactively threshold by using the Density Slice Tool. This is the best method to quantify the breast density (Chow, Venson et al. 2000).

## 2.5 Imaging of breast

### 2.5.1 Mammography

Mammography has been proved to be the single most important breast imaging technique, both for symptomatic or asymptomatic women (Tucker and Ng 2001). This examination is performed as screening in asymptomatic women. There are few criteria needed for patient to be subjected for mammography screening. The criteria for screening according to Malaysian Guideline for screening mammography include high risk women that is women with past history of breast and or ovarian cancer, family history of breast cancer in one or more first or second degree relatives before the age of 50 years and history of atypia on previous biopsy before the age of 40 years, at the discretion of doctors and the wish of patients. In these situations, mammography should be done annually for women age 40-49 years and annually or biennially for women age 50-75 years old. It is also performed in patient before

starting on Hormone Replacement Therapy (HRT) as a baseline investigation and to exclude underlying malignancy or lesion (Malaysia 2002).

Guidelines produced by American College of Radiology, American Medical Association, National Cancer Institute are as below:-

a) Breast self-examination to begin at age 20.

b) Breast examination by physician every 3 years between 20-40 years, in yearly intervals after age 40.

c) Baseline mammogram between 35-40 years of age; follow-up screening based upon parenchyma pattern and family history.

d) Initial screening at 30 years if the patient has first degree relative with breast cancer in pre menopausal years; follow-up screening upon parenchyma pattern.

e) Mammography at yearly interval after age of 40.

f) All women who have had prior breast cancer require annual follow-up.

Diagnostic mammography is performed on women with breast symptoms such as mass, pain, nipple discharge, thickening, skin or nipple retraction and nipple eczema. Another indications include prior to breast surgery, follow up for breast cancer patients and work up for patients with metastases from an unknown primary tumour (G.Grainger and Allison 1999).

Standard mammography is done in two views; cranio-caudal (CC) and mediolateral oblique (MLO) views. Additional views will be taken depending on indications. Magnified view done to further characterized lesions such as micro