THE EFFECTS OF HORMONE REPLACEMENT THERAPY ON MAMMOGRAPHIC DENSITY AMONG POSTMENOPAUSAL WOMEN IN HOSPITAL RAJA PEREMPUAN ZAINAB II, KOTA BHARU, KELANTAN

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Pendahuluan: Rawatan terapi penggantian hormon (TPH) sering di beri kepada wanita menopaus untuk mengurangkan gejala vasomotor. Pengunaan TPH bagi wanita menopaus disabitkan dengan peningkatan ketumpatan pada mammogram dan juga kesan kesakitan pada payudara. Ketumpatan mammogram adalah salah satu risiko yang mengakibatkan kanser payudara.

Tujuan: Tujuan kajian ini adalah untuk menguji kesan TPH terhadap ketumpatan mammogram.

Metodologi: Satu kajian pemerhatian telah dijalankan selama 18 bulan. Seramai 33 wanita yang telah menopaus dan menerima rawatan TPH telah direkrut untuk kajian ini. Prosedur mammogram telah dijalankan sebelum rawatan dimulakan and selepas 12 bulan menerima TPH. Mammogram telah dikaji dan diselidik dengan menggunakan cara klassifikasi

BIRADS. Wanita tersebut juga telah ditemuramah tentang pengalaman kesakitan pada payudara dengan menggunakan skala yang telah ditetapkan.

Keputusan: Perubahan yang ketara dari segi statistik telah direkodkan dengan kajian secara kategorikal seperti cara klassifikasi BIRADS. Terdapat 30.3% wanita yang mempunyai penambahan ketumpatan mammogram dan 33.3% wanita yang mengadu kesakitan payudara selepas menerima rawatan TPH. Perubahan yang ketara dari segi statistik telah direkodkan antara kesakitan payudara selepas rawatan TPH dan penambahan ketumpatan mammogram. Kami juga membuat kesimpulan bahawa fakto-faktor lain seperti umur, jumlah anak, indeks jisim badan, umur sewaktu putus haid dan tempoh putus haid tidak berkait secara statistik dengan peningkatan ketumpatan mammogram.

Kesimpulan: Kajian ini menunjukkan bahawa rawatan TPH menunjukkan perkaitan yang ketara dengan ketumpatan mammogram. Seramai 30.3% wanita yang menerima rawatan TPH didapati mempunyai peningkatan ketumpatan mammogram. Seramai 33.3% wanita yang menerima TPH mengadu kesakitan pada payudara. Peningkatan ketumpatan mammogram juga didapati berkait rapat dengan kesakitan pada payudara di kalangan wanita yang menerima rawatan TPH.

Ass Prof Dr Noreen Norfaraheen Lee: Supervisor

Dr Md Ariff Abas: Co-Supervisor

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evaluated according to BIRADS classification of breast density. During follow-up, patients were also enquired about breast pain and they were asked to classify according to a specified scale.

Result: The categorical assessments showed that there was a significant shift in categorical classification as assessed by BIRADS categories among the postmenopausal women receiving hormone replacement therapy. Amongst these women, 30.3% had increased mammographic density after treatment with HRT. There was also significant association between breast pain and increase in mammographic density. Amongst the study population, 33.3% complained of breast pain after hormonal therapy. We also concluded that the study factors (grade, age, parity, BMI, duration of menopause and age at menopause) did not significantly influence change in mammographic density.

Conclusion: Hormone replacement therapy significantly affects the mammographic density and increased mammographic density was associated with breast pain in women receiving hormonal therapy.

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The Effects of Hormone Replacement Therapy on Mammographic Density among Postmenopausal Women in Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan

By

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Dissertation Submitted in Partial Fulfillment of the Requirement for the Degree of Master of Medicine (Radiology)

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- To my husband, children, family and friends who are my pillar of strength
- Last but not least I would like to thank all the postmenopausal women who participated in this study

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List of Abbreviations

AEC	Automatic exposure control
ASR	Age-standardized rate
BIRADS	Breast Imaging Reporting and Data System
BMI	Body Mass Index
CC	Cranio-caudal
CEE	Conjugated equine estrogen
cm	Centimeter
HRPZ II	Hospital Raja Perempuan Zainab II
HRT	Hormone Replacement Therapy
HUSM	Hospital Universiti Sains Malaysia
keV	Thousand electron volts
kV	Kilovoltage
kVp	Peak kilovoltage
LPPKN	Lembaga Penduduk Dan Pembangunan Keluarga Negara
mAs	Miliamperage per second
mGy	Miligray
MLO	Medio-lateral oblique
Mm	Milimetre

Mo	Molybdenum
MPA	Medroxyprogesterone 17 acetate
MWFC	Ministry Of Women, Family and Community Development
MWS	Million Women Study
NCR	National Cancer Registry
PEPI	Postmenopausal Estrogen/Progestin Interventions
TDLU	Terminal ductal lobular unit
TPH	Terapi penggantian hormon
UK	United Kingdom
WHI	Women Health Initiative

Abstrak (Versi Bahasa Malaysia)

Pendahuluan

Rawatan terapi penggantian hormon (TPH) sering di beri kepada wanita menopaus untuk mengurangkan gejala vasomotor. Pengunaan TPH bagi wanita menopaus disabitkan dengan peningkatan ketumpatan pada mammogram dan juga kesan kesakitan pada payudara. Ketumpatan mammogram adalah salah satu risiko yang mengakibatkan kanser payudara.

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Tujuan kajian ini adalah untuk menguji kesan TPH terhadap ketumpatan mammogram.

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Satu kajian pemerhatian telah dijalankan selama 18 bulan. Seramai 33 wanita yang telah menopaus dan menerima rawatan TPH telah direkrut untuk kajian ini. Prosedur mammogram telah dijalankan sebelum rawatan dimulakan and selepas 12 bulan menerima TPH. Mammogram telah dikaji dan diselidik dengan menggunakan cara klassifikasi BIRADS. Wanita tersebut juga telah ditemuramah tentang pengalaman kesakitan pada payudara dengan menggunakan skala yang telah ditetapkan.

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ketumpatan mammogram. Kami juga membuat kesimpulan bahawa fakto-faktor lain seperti umur, jumlah anak, indeks jisim badan, umur sewaktu putus haid dan tempoh putus haid tidak berkait secara statistik dengan peningkatan ketumpatan mammogram.

Kesimpulan

Kajian ini menunjukkan bahawa rawatan TPH menunjukkan perkaitan yang ketara dengan ketumpatan mammogram. Seramai 30.3% wanita yang menerima rawatan TPH didapati mempunyai peningkatan ketumpatan mammogram. Seramai 33.3% wanita yang menerima TPH mengadu kesakitan pada payudara. Peningkatan ketumpatan mammogram juga didapati berkait rapat dengan kesakitan pada payudara di kalangan wanita yang menerima rawatan TPH.

Abstract (English Version)

Introduction

Hormone replacement therapy (HRT) is commonly prescribed to postmenopausal women to improve their postmenopausal symptoms. Postmenopausal hormone use is associated with increase in mammographic density and increased incidence of breast pain. Mammographic density is an independent risk factor for breast cancer.

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Our purpose was to evaluate the effects of hormone replacement therapy on mammographic density in postmenopausal women in Kota Bharu, Kelantan, Malaysia.

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An observational study was conducted for a period of 18 months. A total of 33 postmenopausal women who received combined hormone replacement therapy (containing estrogen and progesterone) were included as study subjects. Mammograms were performed at baseline and after 12 months of receiving HRT. Mammographic density was evaluated according to BIRADS classification of breast density. During follow-up, patients were also enquired about breast pain and they were asked to classify according to a specified scale.

Result

The categorical assessments showed that there was a significant shift in categorical classification as assessed by BIRADS categories among the postmenopausal women receiving hormone replacement therapy. Amongst these women, 30.3% had increased mammographic density after treatment with HRT. There was also significant

association between breast pain and increase in mammographic density. Amongst the study population, 33.3% complained of breast pain after hormonal therapy. We also concluded that the study factors (grade, age, parity, BMI, duration of menopause and age at menopause) did not significantly influence change in mammographic density.

Conclusion

Hormone replacement therapy significantly affects the mammographic density and increased mammographic density was associated with breast pain in women receiving hormonal therapy.

1.0 Introduction

Menopause is a state of natural ovarian senescence with accompanying oestrogen deficiency. It also refers to states of ovarian failure and ovarian destruction/removal with accompanying oestrogen deficiency. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhoea for which there is no other obvious pathological or physiological cause. Menopause is a universal and irreversible part of the overall aging process involving a woman's reproductive system.

The life span of women has improved significantly in the last two decades. Malaysian women's life expectancy now has reached 76.4 years and for male it is 70.6 years (Department of Statistics Malaysia, 2005). However, the age of onset of menopause has not changed and remained at 50 to 52 years despite improvement in life expectancy of women. This means women will spend nearly one third of their life span in the postmenopausal years. Failure of estrogen production by the ovaries during this period can lead to various changes in their bodies. These changes can be constituted into:

- Early menopause symptoms such as vasomotor instability and psychosexual disturbances
- Late menopause symptoms such as osteoporosis and heart disease

Hormone replacement therapy (HRT) remains the first-line and most effective treatment for menopausal symptoms. However, despite massive, good-quality clinical outcome data on efficacy and safety when HRT is begun for symptoms in the early menopause, many physicians and lay people believe that hormones are risky and undesired even in the most appropriate case scenarios. Many misconceptions and misperceptions play

roles in this complicated situation, some are purely scientific whereas others are cultural or social (Pines, A. et al., 2007).

Prolonged administration of HRT has been associated with a slight but statistically significant increase in the risk of breast cancer. HRT slows normal breast involution and can cause an increase in mammographic density. There have been various studies on the interplay between HRT and breast density. HRT causes increase in mammographic density in up to 25% of women. This increase in density is largely determined by the preparation of HRT and likely to follow prolonged use and use before menopause (Warren, R. 2004).

Mammographic density is one of the parameters evaluated in the mammogram and is best determined by the relative amounts of epithelial tissue, connective tissue and fat in the breast. All non fatty breast tissue e.g. epithelial tissue and connective tissue will appear as white on mammogram and referred to as mammographic densities. The extent of breast density varies widely among women but in general decreases with age especially after menopause (Laya et al., 1995).

The amount of dense tissue in the breast can be assessed either categorically or continuously. Wolfe J. N. was the first to describe four categorical patterns of mammographic density. There are various other methods to classify the mammographic density. Mammographic density has two important implications. A dense parenchymal pattern may be a predictor of breast cancer risk and the density may affect mammographic sensitivity (Leung, w. et al., 1997).

The hormonal environment in which breast cancer develops appears to be revealed by observing mammographic density (Warren, R. 2004). Breast cancer is the commonest cancer for females in Malaysia, with a prevalence of 86.2 per 100,000 women in 1996. Breast cancer mortality rate shows an increasing trend in Malaysia from 0.61 in 1983 to 1.8 per 100,000 women in 1992. Based on the report from the Malaysian National Cancer Registry (NCR) 2003, breast cancer was the commonest cancer in all ethnic groups and all age groups in females from the age of 15 years. The overall age-standardized rate (ASR) was 46.2 per 100,000 populations.

Risk of developing breast cancer is higher among women 50 years and above. Normal ovarian activity increases the risk of breast cancer. An early menarche increases the risk before age 35 years, and a late menopause increases the risk later in life.

Breast pain is common and affects 50 - 70% of all women at some time in their lives. There are different types and patterns of breast pain which normally relate to the underlying cause. The most common pattern is cyclical breast pain which means it shows a definite relationship to the menstrual cycle, almost always pre-menstrual, with a duration varying from a few days, up to four weeks. Another common cause of breast pain is medication containing hormones in them, either contraceptive pills or hormone replacement therapy.

Breast pain is a common side effect of hormone replacement therapy. This is usually attributable to the oestrogen component of the therapy. HRT may cause transient breast tenderness, especially in older women and those furthest from the menopause. Results of the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial and other

randomized controlled trials demonstrate that breast discomfort increases with administration of combined oestrogen and progestin therapy. Postmenopausal women who experience new pain in their breasts while taking hormone replacement therapy may have an increased risk of developing breast cancer. The researchers concluded that new onset breast pain while taking hormone replacement therapy is associated with an increase in breast tissue density. Since breast tissue density is associated with an increased risk of breast cancer, these results indicate that new onset breast pain may ultimately be associated with an increased risk of breast cancer among postmenopausal women taking hormone replacement therapy.

Knowing the above mentioned risks, this study was designed to determine if HRT increases the mammographic density in postmenopausal women and to assess the incidence of increased breast density in postmenopausal women receiving HRT. Many studies have been done in Western countries on effect of HRT on mammographic density but not many similar studies have been done locally. Mammographic density is an independent risk factor for breast cancer. The degree of risk that is associated with mammographic density is greater than the degree of risk that is associated with almost all other known breast cancer risk factors. Knowledge of the variables associated with increased mammographic density may allow greater understanding of the nature and causes of breast cancer. As a result, measurement of mammographic density is useful as a mean of investigating the etiology of breast cancer and to test the hypotheses about potential strategies.

2.0Literature Review

2.1 Mammary gland

The mammary glands are modified skin gland enveloped in fibrous fascia (Moore, K. L. 2005). Mammary gland develops on the chest wall between the clavicle and the sixth to eight ribs. It develops under the influence of estrogens in adolescence to reach its adult size. There are fifteen to twenty lobes in each breast disposed radially around nipple. Each lobule is composed of grape-like clusters of acini (also called alveoli), the hollow sacs that make and hold breast milk. The mammary gland is made up of both fatty tissue and glandular milk-producing tissues (Dahnert, W. 2000).

Most breast cancer is thought to originate in the terminal ductal lobular unit (TDLU). The gland is anchored to the pectoralis major fascia by the suspensory ligaments first described by Astley Cooper in 1840. These ligaments run throughout the breast tissue parenchyma from the deep fascia beneath the breast and attach to the dermis of the skin. Lobes, lobules, and acini serve to produce and secrete milk—the primary function of the breast mammary glands.

Mammary glands receive its blood supply from several sources. The arteries are mainly from the internal thoracic artery via its perforating branches, which pierce the second to fourth intercostals spaces. There is also supply from the axillary artery mainly from its lateral thoracic and thoracoacromial branches as well as the intercostals arteries. The veins correspond to the arteries. The chief venous drainage is to the axillary vein (Moore, K. L. 2005).

The lymphatic system of the breast is of clinical importance in terms of cancerous spread. Lymphatic drainage is primarily via the axilla (97%) with the internal mammary chain accounting for the remaining 3%. The lateral quadrants of the breast drain into the anterior axillary or pectoral nodes. The medial quadrant drains into the nodes along the internal thoracic artery. A few lymph vessels follow the posterior intercostals arteries and drain posteriorly into the posterior intercostals nodes. Some lymphatic vessels communicate with the lymph vessels of the opposite breast (Moore, K. L. 2005)

2.2 Factors affecting breast tissue composition

Glandular tissue and fat vary with a woman's age and weight. The ratio of fatty tissue to glandular tissue varies among individuals. In addition, with the onset of menopause, the relative amount of fatty tissue increases as the glandular tissue diminishes. Increased or decreased glandularity of the breast is a part of the normal physiologic process changes that take place within the breast and is generally mirrored on the opposite breast. It can be related to hormonal fluctuation (whether normal or synthetic) including menarche, pregnancy, lactation or menopause. Increase in glandularity is also dependent on a woman’s genetic predisposition. Although the breast is fully developed by age 20, complete maturation of the breast may not occur until the woman reaches 30 years (Peart, O. J. 2005). The two most important hormones active in breast development are estrogen and progesterone. Estrogen is responsible for ductal proliferation whereas progesterone is responsible for lobular proliferation and growth.

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. On mammograms, these changes are reflected by greater breast density during the luteal phase than during the follicular phase. As women near menopause, the menstrual cycle shortens. Specifically, the follicular phase shortens, with no significant change in the length of the luteal phase. With the reduction of estrogen and progesterone levels after menopause, the cyclic proliferative process becomes quiescent. Lobular tissue regresses, while the more proximal portions of the ductal system remain. The mammographic appearance of the breasts becomes increasingly radiolucent, with about 34% of women aged 75–79 years having fat-replaced breasts compared with only 11% of women aged 25–29 years (Jennifer A. H. and Victor E. B. 2004).

2.3 Mammography

2.3.1 Mammogram

A mammogram is the x ray of the breast made with specific x-ray equipment. A mammogram is the best radiographic method available today to detect breast cancer early. It is ideal and indispensable for women older than 40 years, for whom the risk of breast cancer is increased. The acceptable physical criteria for optimal mammogram are mean optical density of 1.4 to 1.8, high spatial resolution of 10 line pairs per mm, low contrast spatial resolution of 3.2 line pairs per mm and mean glandular dose of 2mGy per view.

The technical requirements for screen-film mammography differ considerable from those for other radiographic studies. Dedicated mammography x-ray equipment is necessary for producing high quality images. Since it contains a phosphor which

converts x-ray energy into light, a screen-film system allows a lower dose than obtained with film alone. The most commonly used target filter combination is a molybdenum target with 0.03mm Mo filter. Soft tissue contrast depends on a relatively low kVp x-ray beam to enhance the differential absorption of fatty, fibroglandular and calcific tissues. The peak kilovoltage is normally in the range of 26 – 30 kV and typically 28 kV. The resultant x ray spectrum exhibits characteristic x rays at 17.4 and 19.4 keV. High resolution is needed to visualize microcalcifications and trabeculae, often as small as 0.1mm. Short exposure times are necessary to prevent motion unsharpness. The focus to film distance is in the range of 60 – 65mm.

Automatic exposure control (AEC) is used in mammography to automatically control the exposure duration so that the optimum optical density of the mammogram is maintained over a wide range of different breast sizes and densities. Moving grid system is used in mammography to improve resolution and contrast by decreasing scattered radiation.

Breast compression is essential to ensure high quality mammograms and is applied using a powered system operated by a foot control. Film compression should be applied to the entire breast. The purpose of even and firm compression is to geometric unsharpness, improve contrast by reducing scatter, diminish motion unsharpness, to reduce radiation dose, to achieve more uniform film density and to separate superimposed breast tissues so that lesions are better seen.

2.3.2 Mammography projections

The standard screen-film mammographic examination consists of a medial-lateral oblique (MLO) and cranio-caudal (CC) view of each breast. Careful positioning is essential for optimal demonstration of breast tissue.

The standard CC view is obtained with a vertical x-ray beam and the breast being compressed between the two plates horizontally. The CC view demonstrates the subareolar, medial and lateral portion of the breast. However, the posterolateral aspect of the breast may be incompletely demonstrated. The antero-posterior distance of the breast should be within 1cm of the length of posterior nipple line. Posterior nipple line is the perpendicular distance from the back of the nipple to the anterior margin of the pectoral muscle on MLO view.

The medial-lateral oblique view is usually obtained with the x ray tube angled between 30 – 60 degrees to the horizontal depending on the built and pectoralis muscle of the women. This is to ensure compression is applied perpendicular to the long axis of the pectoralis muscle. More breast tissue is demonstrated in MLO view than any other views. The nipple should be in profile in MLO view. The pectoralis muscle should be visible down to the level of the nipple, and the axillary tail and inframammary fold should be visible. The breast should not be sagging. The glandular tissue should be evenly compressed and adequately penetrated. There should be no skin folds superimposed on the breast. Patients need to be relaxed to achieve satisfactory positioning.

Supplemental views are occasionally obtained to further evaluate the breast tissue. Magnification views are obtained by increasing the object-film distance to produce an air gap and a fine focal spot is used to increase resolution. A magnification factor of 1.5 is usual and the increased resolution obtained is particularly helpful for detailed analysis of microcalcification and margin of small mass lesions. Localized compression views are obtained by using a small paddle compression device. This is to displace the overlying breast tissue so that better demonstration of the features of the lesion can be obtained.

2.4 Mammographic Density

The tissues of the breast are seen on mammogram in three levels of density – fatty tissue that is lucent, tissues of water density and calcifications (Warren, R. 2004). Fibroglandular tissue is a mixture of fibrous connective tissue and glandular tissue. The tissues of water density comprise glandular tissues which are ductal elements, vessels, stroma and Cooper's ligaments. The degree of density varies between individuals. Fat appear darker on mammogram because it is more radiolucent than fibroglandular tissue. Fibroglandular tissue appears as radio-opaque area and often referred as mammographic density or breast density (Byng et al., 1996).

There are wide ranges of breast appearances on mammogram due to variation in breast compositions. The mammographic picture of the breast varies between women according to the relative amount of fat, connective and epithelial tissues. High amounts of connective and epithelial cells yield an increased density in the mammogram. Variations in mammographic density are associated with ovarian function. Density is

increased in women with an early menarche and also during the luteal phase of the menstrual cycle (Soderqvist G. and Schoultz v. B. 2004). Breast parenchymal density in individual women has also been found to vary with age, menopausal status, parity, height and body weight.

With the reduction of estrogen and progesterone levels after menopause, the lobular tissue regresses. As a result, breasts will appear more radiolucent on mammogram. The breast will continue to become less dense with about 50% of women in their 40s and 65% of women in their 20s have 50% or greater breast density (Stomper et al., 1990).

2.5 Methods of measuring mammographic density

There are many ways to assess the mammographic density, both qualitative and quantitative. Qualitatively the breast parenchyma can be classified using Wolfe, Laszlo Tabar and BIRADS methods. Semi-quantitative assessment was done by Boyd et al., 1992 which was based on visual estimation of the percentage of the breast occupied by breast tissue. Quantitative measurement can be made by computer-aided method (Chow et al., 2000). A number of investigators are trying to devise a means of determining the total glandular content from three-dimensional reconstruction of breast (Shephard J. and Bopp J. 2002). Other investigators are exploring the use of magnetic resonance imaging and ultrasonography for quantifying breast density, although these methods may not prove as useful for widespread use as density information already obtained on the mammogram (Jennifer A. H. and Victor E. B. 2004).

2.5.1 Wolfe Classification

In 1976, Wolfe devised a system of classification of mammograms, based on the extent and pattern of radiologically dense tissue. He classified breast parenchyma on mammogram into four categories based on radiographic appearance (Wolfe J. N. 1976). Wolfe parenchymal pattern is based not only on extent of the densities but also on the characteristics of the densities seen (prominent ducts and dysplasia). The following are the description provided by Wolfe.

- N1 category refers to the parenchyma composed primarily of fat at most small amounts of dysplasia and no ducts are visible.
- P1 category refers to parenchyma composed chiefly of fat with prominent ducts in the anterior portion up to the one-fourth the volume of the breast.
- P2 category indicated severe involvement of the breast with prominent ductal patterns occupying more than one-fourth the volume of breast.
- DY category refers to severe involvement with dysplasia often obscures an underlying prominent ductal pattern.

Nulliparous women and women with family history of breast cancer are those most likely to fall into the P2 and DY categories (Ernster et al., 1980). This classification has been applied inconsistently and has wide range of interobserver agreement. In a 1993 review, (Oza and Boyd., 1993) found that the Wolfe classification had an interobserver agreement of 52%–97% and an intraobserver agreement of 69%–97% (Oza and Boyd, 1993).

2.5.2 Laszlo Tabar Classification

Laszlo Tabar developed a method of classification based on anatomic-mammographic correlation. There are five patterns in this classification.

- Pattern I involve scalloped contours from Cooper's ligaments and evenly scattered terminal ductal lobular units (TDLU) as 1-2 mm nodular densities on the mammogram. There are also oval shaped lucent areas corresponding to fatty replacement in this pattern.
- Pattern II represents complete fatty replacement of the breast.
- Pattern III is the combination of retroareolar prominent duct pattern due to periductal elastosis and fatty involution.
- Pattern IV demonstrates extensive nodular and linear densities throughout the breast. The linear densities are due to periductal elastic tissue proliferation with fibrosis called fibroadenosis. The scattered nodular densities of 3-7mm are due to proliferating glandular structures and enlarged TDLU referred as adenosis.
- Pattern V consists of homogeneous, uniformly dense parenchyma with smooth contour due to extensive fibrosis.

In terms of risk of developing breast cancer, patterns I to II are considered as low risk group and patterns IV and V are considered as high risk group.

Gram et al reported that the overall agreement on high risk versus low risk for Tabar and Wolfe classification was 55% with k value of 0.23. This indicates a poor agreement between these two classifications (Gram I. T., Funkhouser E. and Tabar L. 1997). The study also showed that the strength of association between high risk mammographic

patterns and the three selected breast cancer risk factors e.g. parity, number of children and age at first birth, was of greater magnitude when the Tabar instead of the Wolfe classification was applied. Tabar classification also appears to be more closely related to breast cancer risk factors among perimenopausal women compared to Wolfe classification.

2.5.3 BIRADS Density Categories

In the United States, Breast Imaging Reporting and Data System (BIRADS) is used in mammographic reporting to standardize mammography reporting terminology and recommendation categories. Density classification is also included in the BIRADS reporting to inform referring physicians of the decline of sensitivity of mammography with increasing breast density. The four categories used in the BIRADS are almost entirely fatty, scattered fibroglandular densities, heterogeneous density and extremely dense. The advantage of BIRADS is that it is used by practicing radiologists. PEPI trial found that they were highy reliable with inter-observer agreement ranging from 70% to 90%.

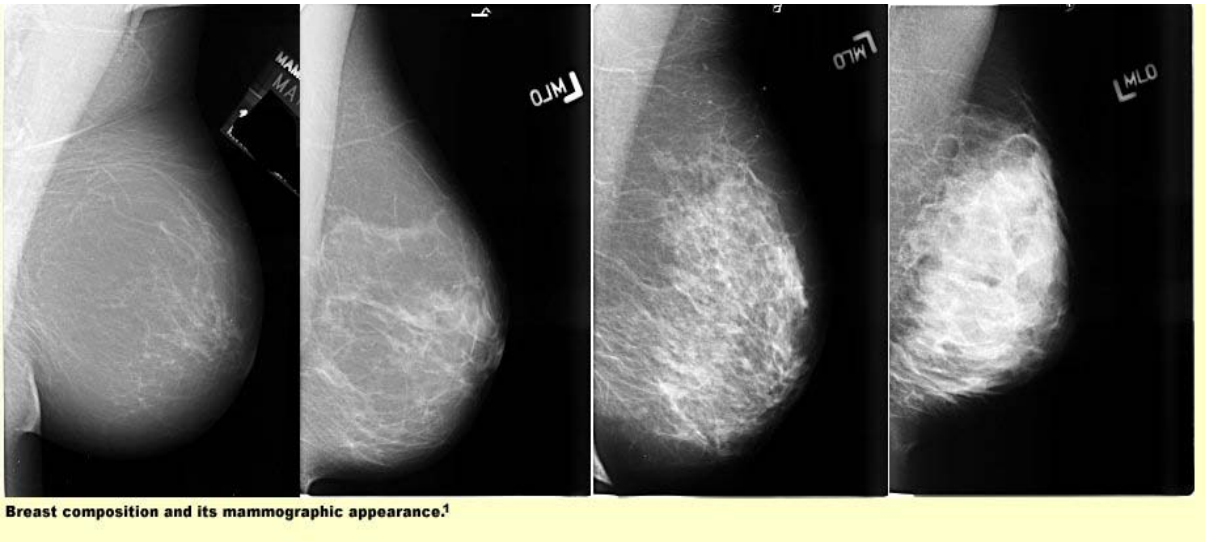

Figure 5-1 Mammography based on BIRADS classification

(Adapted from Interactive Mammography Analysis Web Tutorial – Internet)

2.5.4 Percentage categories

Visual estimation of the percentage of the breast occupied by the fibroglandular tissue has been used frequently. In a study conducted by Stomper et al, parenchymal density on mammogram was assessed visually and was categorized as less than 10%, 10% - 49%, 50% - 89% and 90% or greater dense tissue. The subcutaneous and retromammary fat regions in each breast were excluded during the determination of dense tissue. In patient with asymmetric tissue, the breast with greater density was categorized (Stomper et al., 1996).

Boyd et al proposed a five categories systems which are <10%, 10% - 25 %, 25% - 50%, 50% - 75% and≥75%. In this study, the reliability of this classification was assessed by rereading 100 images. Boyd reported intraclass correlation coefficient of 0.94 for repeated reading. This indicates high degree of reliability (Boyd et al., 1995).

2.5.5 Radiographic method

Breast glandularity could also be determined from radiographic data e.g. tube potential (kV), tube loading (mAs) and compressed breast thickness. Radiographic data was collected by exposing different thickness of phantom material of varying glandular and adipose compositions at 27 kV. Then a fitted equation was derived and applied to calculate breast glandularity. In the study conducted by Jamal at al using this method, the average breast glandularity of Malaysian women was 48.9% (Jamal et al., 2004).

2.6 Hormone replacement therapy (HRT)

The preventive effect of HRT on postmenopausal bone loss and cardiovascular disease as well as alleviating effect on climacteric symptoms is well established (Ozdemir et al., 1999). Clinical trials consistently demonstrate that HRT effectively relieves menopausal symptoms in most women and provides clinically significant long-term beneficial effects as well (Rozenberg, S. 2001). Many different hormone regimens are used including estrogen, estrogen in cyclic combination with a progestogen and estrogen in continuous combination with a progestogen (Topal et al., 2006). Current HRT regimens combine continuous estrogen with continuous or sequential progestogen to achieve the beneficial effects of estrogen while avoiding the increased risk of endometrial cancer. Placebo controlled studies have shown that estrogen is effective for post menopausal vasomotor and urogenital symptoms (Drife, 2005). Estrogen only therapy is only recommended for women without a uterus.

Traditional HRT regimes of continuous estrogen and either continuous or sequential progesterone are sometimes associated with troublesome progesterone-related side effects, which may cause women to stop treatment before long-term beneficial effects on osteoporosis or cardiovascular disease can be realized (Breckwoldt M., Keck C. amd Karck U. 1995). The major reasons for early discontinuation and low patient compliance with HRT include the fear of cancer, the return of menstrual bleeding with sequential regimen and also occurrence of premenstrual syndrome-like symptoms (Rozenberg, 2001).

Controversies about the safety of different postmenopausal hormone therapies started 30 years ago and reached a peak in 2003 after the publication of results from the Women Health Initiative (WHI) trial and the Million Women Study (MWS) (Topal, N et al., 2006). WHI study found increased risks of venous thromboembolism, cardiovascular disease, stroke and breast cancer with the use of continuous conjugated oral estrogen with medroxyprogesterone acetate (MPA). The limitations of the trial who studied 16,000 postmenopausal women are that they included older women who were postmenopausal for many years whose results may not extrapolate to a younger menopausal woman (Dull, P. 2006). Million Women Study studied the prevalence of breast and uterine malignancies among users and non users on HRT. The study revealed an increased risk of breast cancer with long term therapy of estrogen (Dull, P. 2006).

In light of the findings of these large scale studies, concerns were raised about the safety of HRT use and this caused anxiety and concern to both medical professionals and the public. There is currently consensus that HRT is justified for the relief of symptoms but not for the prevention of chronic disease after the menopause (Drife, J. 2005). The

College of Obstetricians & Gynaecologists and Academy of Medicine of Malaysia produced an updated Clinical Practice Guidelines (CPG) in July 2010 which recommends that initiation of HRT should be done in relation to proximity to menopause. Thus, it is best to start HRT between the ages of 50-59 years, or within 10 years of the menopause. After the age of 60 years, HRT should not be initiated unless there is a compelling indication. For those with premature menopause, HRT should be recommended and started as soon as possible.

Tibolone, a tissue-specific compound, constitutes an alternative for treatment in postmenopausal women (Moore R. A. 1999). After oral intake, tibolone is rapidly converted into 2 estrogenic metabolites and its isomer, which has progestogenic and adrogenic activities (Lundstrom et al., 2002). As well as relieving vasomotor symptoms, tibolone has positive effects on sexual well-being and mood, and improves vaginal atrophy and urogenital symptoms. Prevention of bone loss is comparable to that seen with estrogen therapy and estrogen-progestrone therapy (Kenemans P. and Speroff L. 2001). As tibolone rarely causes endometrial proliferation, no additional progesterone is needed. It also has good tolerability, being associated with a low incidence of vaginal bleeding and of breast pain (Kenemans P. and Speroff L. 2001).

2.6.1 Hormone replacement therapy and breast cancer

Controversies about the safety of different postmenopausal hormone therapies started 30 years ago and reached a peak in 2003 after the publication of results from the Women Health Initiative (WHI) trial and the Million Women Study (MWS) (Topal et al., 2006). While there are contradictory findings, epidemiological data overall indicate

an increase in the risk of breast cancer during hormonal therapy (Soderqvist G. and Schoultz v. B. 2004). The pathophysiological mechanisms behind the association between risk and ongoing treatment are incompletely understood.

The interpretation of available data is complicated by a lack of basic understanding as to how hormones work in the normal breast. HRT is not a uniform concept and a wide range of different estrogens and progestogens are available on the market and used at different doses, combinations and by different routes of administration. Estrogen is a well known mitogen in human breast epithelium but the action of progestogen is complex and incompletely understood (Soderqvist G. and Schoultz v. B. 2004). The basis of breast cancer risk associated with hormonal therapies may lie in the regulation of cell proliferation (Humphrey, L. L. et al., 2001).

In the Million Women study in the UK, the relative risk of breast cancer between current HRT users and non-users was compared. Roughly one million women aged 50-64 years participated in the study between 1996 and 2001. The result indicates that HRT is indeed associated with an increased risk of incident and fatal breast cancer especially for combined estrogen and progesterone therapy. Current users of HRT at recruitment were more likely than never users to develop breast cancer and die from it. However, past users of HRT were not an increased risk on incident of fatal disease. In current users, the risk of breast cancer increased with increasing total duration of use. Ten years use of HRT is estimated to result in five additional breast cancers per 1000 users of estrogen only preparation and 10 additional cancers per 1000 users of estrogen-progestin combinations. The relative risk for breast cancer was 1.3 in users of estrogen

alone, 1.45 in tibolone users and 2.0 in women on oestrogen combined with progestin (Beral, 2003).

A large meta-analysis was done in 1997 questioning a link between HRT and breast cancer risk which studied 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. This study found that the excess risk increases with the duration of use and disappears 5 years after stopping treatment (Colloborative Group in Hormonal Factors in Breast Cancer, 1997). A local study done in Kelantan by Norsa'adah et al found no significant association between HRT and breast cancer (Norsa'adah et al., 2005). The failure to detect the association may be related to the low uptake of HRT among post-menopausal women in Malaysia.

2.7 Relationship between HRT and mammographic density

Mammographic changes associated with hormone replacement therapy were first reported by Peck and Lowman in 1978 (Cyriak, D. 1993). These changes include a generalized increase in mammographic density, developing densities and enlarging benign masses such as cysts and fibroadenomas (Evans, A. 2001). It has been suggested that the use of estrogen alone may be associated with focal changes and the use of combination therapy with a diffuse increase in density HRT (Litherland, J. C. et a., 2000). This can significantly adversely affect both the sensitivity and specificity of screening mammogram. According to (Erel et al., 1996) cessation of HRT resulted in regression of these mammographic findings.

Hormone replacement therapy (HRT) slows normal breast involution and causes an increase in mammographic density in women. The response of HRT depends on the individual woman and is neither necessarily uniform nor global. The increase in density is most commonly diffuse but may be focal or multifocal (Litherland, J. C. et al., 2000). It depends on the hormonal receptivity of the epithelial elements. There have been numerous studies done on the interplay between HRT and breast density which vary in quality and scope (Warren, G. 2004). Mammographically dense breasts reflect a high proportion of stromal, ductal and glandular tissue (Speroff, L. 2002).

Various studies show that increase in breast density varies widely between 17% to 73%, depending on the method of assessment of changing density. However, when standardized, pre-agreed categories are used by reporters, figures fall in the range of 17% - 24% indicating that the majority of HRT users do not have demonstrable change as a result of taking HRT (Litherland, J. C. 2000). The effect of endogenous and exogeneous hormones on the breast is a complex and so is the study of the effect of HRT on breast. The variety of drugs, drug dosage, drug combinations, routes of administration, duration of use, patient compliance, changes in drug type and dosage in long-term users , and the status of the breast at the time HRT is started contributes to the complexity.

In clinical practice many different therapeutic regimens are used for hormonal replacement. The increase in mammographic density associated with HRT use varies according to the type of HRT preparation used (Evans, A. 2001). The type of treatment for hormone replacement depends on patient preference, compliance, conditions such as

previous hysterectomy allergy to transdermal preparations or gastrointestinal intolerance to oral preparations, besides the physician's choice (Ozdemir et al., 1999).

Most studies show that combination hormones regimens increase mammographic density more often than estrogen only regimens (PEPI trial, 1999). Studies on breast morphology indicate that although the sites of their primary effects are somewhat different, both estrogen and progesterone stimulate breast cell division. However the mitotic rate of breast cells is higher during the luteal phase of the menstrual cycle than during the follicular phase, suggesting that progesterone and estrogen induce more mitoses than estrogen alone (Clarke C. L. and Sutherland R. L. 1990).

Estrogen promotes growth of the ducts by causing proliferation and differentiation of mammary duct epithelium. Progesterone acts in synergism with estrogen on the distal portion of the ducts, favoring differentiation into acini, and promotes growth of lobuloalveolar structures. As ductal, periductal connective, and lobular tissue proliferates in response to a combination of estrogen and progesterone, the greatest increase in mammographic breast density would be expected in women being treated with the combination of estrogen and progesterone (Cyrlak and Wong, 1993).

In 1990, Stomper et al reported that mammographic changes developed in 24% of postmenopausal women undergoing hormone replacement therapy. Changes were seen more often in women treated with the combination of estrogen and progesterone (26%(than in women treated with estrogen alone (17%). In another study done by (Berkowitz et al., 1990), 17% of women had mammographic changes while undergoing hormone replacement therapy. (Laya et al., 1995) showed that combined estrogen and

progesterone HRT resulted in a significant increase in the percentage of mammographic densities and change in parenchymal pattern in sizeable proportion of postmenopausal study subjects. After 1 year of treatment with continuous combined HRT in this study, there is upward shift of 24% in Wolfe classification and 73% increase in density percentage over baseline with magnitude of change of 10% or more over pretreatment values. This study also showed that density increase was most pronounced in those women with a lower baseline density (Laya et al., 1995).

Another study done in 1999 at 7 Unites States centres involving 307 women showed significant increase in density within 1 year of use of combined preparation of HRT (Greendale et al., 1999). A prospective observational study done in Turkey showed that density changes are dependent of the HRT regimen and formation of cysts and solid lesions are not related to HRT (Ozdemir et al., 1999). Correlating with this is the findings of the Swedish study done by (Lundstrom et al., 1999) which showed that different preparations have different effects on breast density (Lundstrom et al., 1999). A 1998 consensus document concluded that the incidence of increased mammographic density was as much as twice as high with continuous combined HRT (up to 30%) compared with cyclic combined HRT (up to 15%) (Junkermann et al., 2004).

A large scale study involving 1232 women was done in Ontario, Canada comparing HRT users and non-users. This study showed that density decreases after age 55 in non-users of HRT, but not so in HRT users. In some women, density decrease continues on HRT suggesting they are refractory to the effect of hormone. Increased density was seen in less than 8% of women. They concluded that adverse effect may depend on receptivity of epithelial elements (Sterns and Zee, 2000). El-Bastawissi et al conducted

an observational study on 28984 HRT users and non-users which showed that HRT has transitory association with breast density (El-Bastawissi et al., 2001).

A Swedish study done in 2002 showed the risk of density increase to be 10% for estradiol compounds and 28% for combined estradiol and progestin compounds. Increase in density is particularly common in women taking continuous combined preparations compared to women taking cyclical combined preparations. Several studies done show that different regimen have different effects on density, combination of estrogen-progesterone have more effect than other forms (Persson L., Thurfjell E. and Holmberg L. 1997, Lundstrom et al., 1999, Sendag et al., 2001, Erel et al., 2001, Lundstrom et al., 2002, Bulbul N. H., Ozden S. and Dayicioglu V. 2003, Vachon et al., 2002, Greendale et al., 2001). Conjugated equine estrogens (CEE) alone did not affect mean mammographic percent density of women enrolled on the randomized, placebo controlled Postmenopausal Estrogen/Progestin Intervention (PEPI) trial. However, women who were randomly assigned to CEE/progestin combination treatment arms had mean increases in density that ranged from 3% to 5% (Greendale et al., 2001).

Many large scale studies done across the globe show that HRT is associated with an increase in mammographic density in a significant portion of postmenopausal women. Several studies show that the increase occurs within the first year of use of starting HRT and diminishes within 3 weeks after stopping (Warren, R., 2004). According to (Marchesoni et al., 2006), the breast density increase quickly at the beginning of the hormonal therapy and decrease quickly at the end of the therapy (Marchesoni et al., 2006). Breast density change during HRT is dynamic, increasing with initiation and decreasing with discontinuation and change of therapy (Soderqvist G. and Schoultz v.