HORMONE RECEPTOR STATUS OF BREAST CANCERS AND OTHER PROGNOSTIC FACTORS IN TWO STUDY CENTRES

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7. ABBREVIATIONS

AJCC	American Joint Committee on Cancer
BSE	Breast self-examination
DCIS	Ductal carcinoma in situ
ER	Estrogen receptor
FISH	Fluorescence in situ hybridization
FNAC	FNAB - Fine needle aspiration cytology
HER2	Human Epidermal growth factor Receptor
HRT	Hormone replacement therapy
IDC	Infiltrating ductal carcinoma
LCIS	Lobular carcinoma in situ
OCP	Oral contraceptive pill
PR	Progestrone receptor
SERMs	Selective estrogen receptor modulators
SCLN	Supraclavicular lymph node
TNM	Tumour Node Metastases

8. ABSTRAK

PENGENALAN

Barah payudara di Malaysia merupakan kanser paling kerap menyerang wanita tanpa mengira kaum dan berlaku pada peringkat umur lebih muda berbanding pesakit di negara maju. Penyebab kematian barah ke empat tertinggi di Malaysia dan pesakit yang dikesan berperingkat teruk dengan saiz ketumbuhan besar dan dalam peringkat akhir barah.

Terdapat banyak barah bereseptor-negatif dan bergred histopatologi tinggi di Asia berbanding dengan negara-negara maju mengundang persoalan sama ada kewujudan pola berlainan pada barah payudara di Asia.

OBJEKTIF KAJIAN

Tujuan kajian adalah menentukan kewujudan hubungan antara umur pesakit dengan status reseptor barahnya. Hubungan antara status reseptor barah dengan faktor-faktor prognostik lain seperti saiz barah, status kelenjar ketiak, gred barah juga dikaji.

TATACARA

Kajian retrospektif melibatkan 160 pesakit didiagnosa dari 1 Januari 2003 hingga 31 Disember 2008. Senarai nama didapati dari senarai pendaftaran kanser Jabatan Patologi Hospital Raja Perempuan Zainab II (HRPZ II) dan Hospital Universiti Sains Malaysia (HUSM). Maklumat-maklumat tersebut kemudian didapati dari buku-buku catatan perubatan di Unit Rekod dan dianalisa dengan perisian komputer SPSS, versi 12.0.

KEPUTUSAN

Kajian mengenalpasti perhubungan antara saiz barah, kehadiran kelenjar ketiak dengan tahap keterukannya. Kebanyakan pesakit berumur di antara 40 hingga 49 tahun. Sedikit sahaja yang bersaiz barah 2 cm dan ke bawah semasa didiagnosa. Tahap II dan gred III merupakan tahap paling banyak dikesan. Hanya 47.8% ialah ER positif dan 51.5% ialah PR positif.

KESIMPULAN

Kajian tidak dapat membuktikan hubungan keterukan barah dengan umur dan status reseptornya. Kebanyakan pesakit yang bersaiz barah besar bergred histologi yang tinggi, berreseptor negatif dan kelenjar ketiak yang positif barah.

9. ABSTRACT

In Malaysia, breast cancer is the commonest cancer in all ethnic. Breast cancer in Malaysian women occurs in the younger age group compared with Western countries and the fourth most common cause of death among all cancers in Malaysia. Stage at presentation here is more advanced with tumor size being much larger and with either locally advanced or metastatic breast cancer. There was a higher proportion of hormone receptor-negative with higher grade tumour in Asian patients compared to Western countries raises questions whether a different pattern of breast cancer is seen in Asian.

OBJECTIVES

The aim of this study is to evaluate the age at presentation and hormone receptor status of breast cancers and its association with other established prognostic factors for example tumor size, lymph node status and tumour grade.

METHODOLOGY

This is a study of retrospective record review of 160 patients diagnosed from 1st January 2003 to 31st December 2008. List of name of patients have been obtained from cancer registry of Pathology Department in Hospital University Sains of Malaysia (HUSM) and Hospital Raja Perempuan Zainab II (HRPZ II). The data were obtained from medical

records. Data were entered into data collection protocol and were analyzed using SPSS software version 12.0.

RESULTS

This study identifies the association between tumour size and lymph node involvement and staging of breast cancer at presentation. Majority breast cancer patients in this study were from 40 to 49 years old. Minority of patients had tumour size 2cm and below at presentation. The commonest stage at presentation of breast cancer was at stage II and grade III. Only 47.8% were ER (+) and 51.5% were PR (+) respectively.

CONCLUSION

This study cannot prove of association between young age and receptor status with advanced stage of breast cancer. Majority of patients presented with large size tumour with poorly differentiated histology, estrogen receptor-negative and lymph node metastases.

CHAPTER 1: INTRODUCTION

Breast cancer is the commonest cancer in all ethnic groups and all age groups in Malaysian females from the age of 15 years. National Cancer Registry 2004 reports breast cancer was the most frequent cancer among females in Peninsular Malaysia (31%) followed by cervix uteri cancer (12.9%) and colon cancer (6%) (Lim and Yahya, 2004). Furthermore it was the fourth most common cause of death among all cancers in Malaysian with ranged from 7.0% to 7.5% (Hisham and Yip, 2003).

Figure 1.1: Example case of locally advanced left breast cancer treated at HRPZ II (photograph taken by the author after consented by patient)

In general, breast cancer in Malaysian women occurs in the younger age group with peak prevalence between 40 and 49 years of age compared with Western countries (between 50- to 59-year-old age group) (Hisham and Yip, 2003). He also reported the stage at presentation here is more advanced with tumor size is much larger and with

either locally advanced or metastatic breast cancer (Figure 1.1). This was supported by a recent report of similar finding by Agarwal *et al* (2007). He found that the pathology and clinical pictures of breast cancers in young Asian women are different from those of average patients managed elsewhere in the world. Lim *et al* (2007) showed a clinico-pathologic feature of breast cancer in Singaporean women differs from what have been observed in the Caucasians. Patients present here at a younger age, with more advanced stage and fewer estrogen-positive tumors. The aggressive behaviour of breast cancer, particularly when it occurs in younger women with negative estrogen receptor status, raises more questions than answers whether a different pattern of breast cancer is seen in Asian. Furthermore most of the studies of breast cancer were done in Western region.

There were a few studies done regarding breast cancer among Malaysian population. Hisham *et al* (2004) reported that only a small number of published data of breast cancer on the race, age and stage at presentation in our country. Furthermore, lack of national cancer registry in Malaysia cause a difficulty in determining the exact breast cancer incidence in Malaysia (Hisham and Yip, 2004).

Kelantan is one of fourteen states in Malaysia federation. It is situated at the north-east coast of Peninsular Malaysia. The state is facing the South China Sea and it covers a land area of 14,922 sq km. Kelantan has an estimated population of 1.37 million. It is a state with a majority Malay ethnic group, comprising ninety five percent of the population, followed by Other Bumiputras (2%), Chinese (1.5%) and Indian (1%) of population (Kelantan Tourism Information Center 2010). Because of small numbers of

non-Malay patients, it would be difficult to analyze these clinical observations according to ethnicity; therefore all patients were analyzed as a group.

Hospital Raja Perempuan Zainab II (HRPZ II) and Hospital Universiti Sains Malaysia (HUSM) are situated in the center of Kelantan. Both hospitals are the main public tertiary referral centres in the state that offers management of breast carcinoma. HRPZ II is managed under Ministry of Health and HUSM is under Ministry of Higher Education. HUSM usually receive referral cases from districts of Bachok, Pasir Puteh, Besut (Terengganu) and occasionally receive referral from Setiu, Terengganu. HUSM is the only hospital in Kelantan that offers radiotherapy and oncology services. HRPZ II received referral from other district hospitals.

Tumour size, lymph node status, histological grade, mitotic index, estrogen receptor (ER), progesterone receptor (PR), c-erbB2, p53 and MIB-1 proliferation index are known as prognostic factors used for breast cancer (Aryandono *et al.*, 2006). The estrogen and progesterone receptor examination is recommended especially for predictor of response to hormonal treatment (Aryandono *et al*, 2006).

The aim of this study is to evaluate the age at presentation and hormone receptor status of breast cancers in Kelantan and Besut district of Terengganu and its association with selected established prognostic factors. Breast cancers were studied clinically, pathologically and immunohistochemically for age at presentation, tumor size, lymph node status, estrogen receptor, progesterone receptor. The associations of ER and PR with those prognostic factors are determined.

I hope that the result of this study will enrich the literature on various aspect of breast carcinoma in our local setting. It also can predict on the progression of patients after the primary cancer treatment.

2.1 HISTORY OF BREAST CANCER

Breast cancer may be one of the oldest known forms of cancerous tumors in humans. It already recorded in document ancient word for more than 5000 years (Sakorafas, 2001). The oldest description of cancer was discovered in Egypt stated in The Edwin Smith Surgical Papyrus, which probably dates back to the pyramid age of (3000–2500 BC) and is believed to contain the first reference to breast cancer.

Herodotus (484–425 BC) claimed a Persian physician living in Greece, cured the wife of Persian King Darius of a breast tumor that had ulcerated and spread. Hippocrates (460–375 BC) described cases of breast cancer with bloody discharge from nipple and he noted that when the discharge stopped, the patient died (Donegan, 2002).

In the Renaissance era, Andreas Vesalius (1514 ± 1564) has treated breast cancer by wide local excision (Sakorafas, 2001). Charles Moore (1821–1870) recommended removal of axillary nodes and the pectoral muscles if they were involved with breast cancer. William M. Banks in Liverpool carried mastectomy by practicing routine removal of axillary lymph nodes (Donegan, 2002). Richard von Volkmann and Lothar Heidenheim in Germany proposed the removal of the pectoralis major muscle fascia en bloc with the breast and the axillary lymph nodes.

William Halsted (1852–1922), professor of surgery at Johns Hopkins Hospital in Baltimore, USA was aware of it. He started what became known as the radical mastectomy. He removed whole breast tissue, the pectoralis major muscle, pectoralis minor muscle and the axillary lymphatics. This procedure became known as the classic Halsted radical mastectomy. This result with a dramatic fall in local recurrence to 6% compared with the 56–81% reported in Europe (Sakorafas, 2001; Donegan, 2002).

The Halsted radical mastectomy usually causes long-term pain and disability although was seen as necessary in order to prevent the cancer from recurring. In 1948, Patey and R. S. Handley in London proposed "conservative" radical mastectomy. They felt that removal of the pectoralis major did not add to the value of surgical treatment with radical mastectomy. It is also justified to preserve the pectoralis major muscle unless it was directly involved by cancer. This operation finally prevails in 1979 as the "modified" radical mastectomy by both Hugh Auchincloss Jr. and Madden.

This modified radical mastectomy is further modifed by preserving both the pectoralis major and the pectoralis minor muscles (Sakorafas, 2001; Donegan, 2002). This procedure become standard surgical treatment of breast cancer in view of local control and survival rates achieved with modified radical mastectomy were comparable to those for the Halsted radical mastectomy (Sakorafas, 2001).

2.2 BRIEF MANAGEMENT OF BREAST CANCER

Breast cancer is the abnormal growth of cells in the breasts, which leads to the development of malignant tumours. Most common origin of breast cancer is from inner lining of milk ducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas and originating from lobules are known as lobular carcinomas.

2.2.1 Triple assessment

There are increasing rate of breast cancer and most rapid increase are from developing countries as the result of 'westernisation' of lifestyles (Bray *et al* 2004). Breast lump is the most common presenting symptom to breast clinic. The other symptoms of breast cancer are changes in the size of the breast, breast pain, changes on the skin of breast, nipple discharge or nipple retraction. Usually patients will review as outpatient setting with triple assessment approach. This is an ideal approach for patient with suspicious breast lump which assess the clinical, histopathological, and radiological.

After detailed history, physical examination, and mammography, patients will undergo fine needle aspiration cytology (FNAC) procedure or tru-cut biopsy. FNAC and tru-cut biopsy is the diagnostic tool of breast cancer. FNAC is performed by the histopathologist while tru-cut biopsy is performed by surgical medical officer or by surgeon. Histopathology results will be reviewed by surgical team and discussion regarding mode of treatment explained to patients.

FNAC has a sensitivity of 90% and specificity close to 100% (Bdour *et al*, 2008). It is a useful test because it is fast, cheap and less invasive. (Lieske *et al*, 2006). Unfortunately it has percentage of uncertainty and certain surgeons are reluctant to accept FNAC reports as basis for ultimate diagnosis because it lack of important information about the histopathological type, grade, receptors, and intrinsic behavior of the tumor (Bdour *et al*, 2008).

Tru-cut biopsy is now considered to be the standard in the preoperative assessment of breast cancer. In certain place for example in the United Kingdom, tru-cut biopsy has largely replaced FNAC (Lieske *et al*, 2006). It is superior to FNAC in confirming breast cancer in suspicious lumps because it is more accurate with the sensitivity of 97%, and specificity 100%. It is able to give histological diagnosis and further information about tumor type, grade, lymph vascular invasion, and receptors status (Bdour *et al*, 2008). This information is great importance to provide reliable information for preoperative evaluation to improve in the pre-surgical decision-making and allows the use of preoperative adjuvant therapy (Bdour *et al*, 2008).

Patients diagnosed to have breast cancer will be informed of advantages and disadvantages of each treatment and subsequently decided on the definite therapeutic treatment. All these information are important for preoperative evaluation by both surgeon and oncologist either for neoadjuvant treatment or adjuvant treatment of breast cancer. For adjuvant therapy of breast cancer, surgical intervention is the first modalities of treatment. Surgical procedures consisted of modified radical mastectomy or breast conserving treatment.

2.2.2 Post operative management

Post operative histopathology report on histological type, histological grade, lymphovascular invasion, pathological tumour size, number of lymph node involvement, hormonal receptors status (estrogen and progesterone receptors), c-erb B2 status, resection free margin of breast cancer will be reviewed and patients will be further investigated for staging either by computed tomography scan (CT scan), ultrasound or bone scan.

Post operative treatment of breast cancer is based on the post operative histopathology report and staging. It is a multidisciplinary treatment and consists of chemotherapy, radiotherapy, hormonal therapy, immune therapy and supportive therapy. Standard chemotherapy used is combination cyclophosphamide, adriamycin and 5-fluorouracil (CAF regime) or cyclophosphamide, methothrexate and 5-fluorouracil (CMF regime). For more aggressive tumour, a taxane drug, such as docetaxel, is used for chemotherapy.

Radiation is usually added to the surgical bed for resection margin involvement of breast cancer. Monoclonal antibodies, such as trastuzumab (Herceptin), are used for cancer cells that have the HER2 mutation. Breast cancers with positive estrogen receptor hormone receptors will be started on selective estrogen receptor modulators (SERMs) for example tamoxifen. For patients with presented with locally advanced inoperable tumors, neoadjuvant chemotherapy was used for down size of breast cancer

2.3 BRIEF ANATOMY AND PHYSIOLOGY OF BREAST

Breasts or mammary gland are specialized accessory glands of the skin able of producing and secreting milk. The shapes are various. At puberty, breast will gradually enlarge and assume their hemispherical shape by influence of the ovarian hormones on the mammary glands. The ducts elongate and the increase size of the glands is mainly from deposition of fat (Snell, 1992). Usually nulliparous women have a hemispherical shape, while those of multiparous women are broader and pendulant. In old age, the breast volume decreases and it becomes less firm, flatter and pendulant (Macéa, 2006).

Despite individual variation in size and volume, the extent of the base of the breast is fairly constant (Sinnatamby, 2001). The base of the breast extends superiorly from the level of the second rib to inferiorly as far as the level of the sixth or seventh ribs and from the lateral margin of the sternum to the midaxillary line (Snell, 1992).

A non-lactating breast weight ranges from 150 to 225g, while a lactating breast may go beyond 500g in weight (Macéa, 2006). Each breast consists of 15-20 lobes, which spread out from the nipple (Snell, 1992). Strands of fibrous tissue (forming the suspensory ligaments of Cooper) attach the dermis of the overlying skin to the ducts of the breast. The suspensory ligament of Cooper helps to preserve the protuberance of the young breast.

Breast become atrophy and pendulous with increasing age and when contracted by the fibrosis associated with certain carcinoma of the breast, they cause dimpling of the overlying skin. Malignant involvement of dermal lymphatics will cause pitting of the oedematous skin (an appearance often referred to as peau d' orange) (Sinnatamby, 2001). The lymphatic drainage of breast is of clinical importance because of spread of the malignant cells along the lymph vessels (Snell, 1992). Seventy five percent of the lymphatic drainage of the breast passes to axillary lymph nodes, mainly to the anterior nodes, even though direct drainage to central or apical nodes is possible.

There are possibilities of direct drainage from the breast to inferior deep cervical (supraclavicular) nodes. These minor pathways tend to pass on lymph from the breast when the major channels are blocked by malignant disease (Sinnatamby, 2001).

Blood supply to the breast is derived mostly from the lateral thoracic artery. The various supplying vessels create an anastomosing network. Venous drainage pathway to posterior intercostals veins provides an important link to the internal venous plexus vertebral veins and hence a pathway for metastatic spread to bone (Sinnatamby, 2001).

Progesterone and estrogen hormones are the important regulators in reproductive activity of women. They are ovarian steroid hormones and play a role in the development and function of the mammary gland, uterus and the ovary (Gao *et al*, 2002). It has been demonstrated that estrogen hormone controls the early ductal morphogenesis of the mammary gland, whereas progesterone hormones controls ductal branching and alveolar development of the mammary gland during pregnancy (Gao *et al*, 2002).

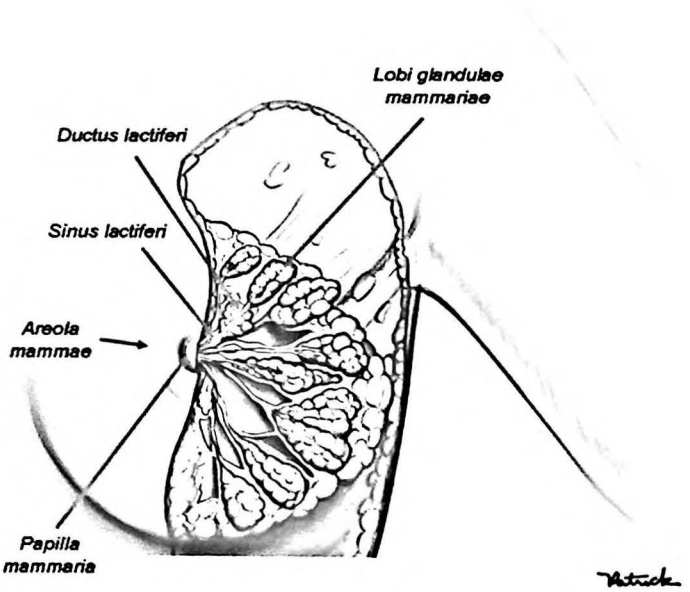

Figure 2.1 Anatomy of left breast (Adapted from Macéa, 2006).

2.4 BREAST FEEDING AND HOLY QUR'AN

Breast-feeding has shown to have protective effect against development of breast cancer and this protective effect is only valuable after prolonged breast feeding. It is potentially adjustable behaviour and represents one of the opportunities for intervention at present. There are variation of incidence of breast cancer which is markedly lower among populations in which breast-feeding is the most common and the most prolonged (Lipworth *et al,* 2000). Breastfeeding is a normal practice and culture to many Asian women. Breastfeeding is related to socio-economic status, educational level, employment and marital status of the women.

2.4.1 Breast feeding and Holy Quran

Breast feeding is encouraged by Islamic teaching: In Sura Al-Ahqaf, it is mentioned; "*the carrying of the (child) to his weaning is (a period) of 30 months*". In verse 14 of Surat Luqman: Quran establish the period of lactation with almost two years. "*And We enjoined on man concerning his parents- his mother bore him in weakness upon weakness, and his weaning was in two years.*" (31:14). This similar with agreement with modern scientific finding where the maximum period of breast-feeding is two years (Khattak *et al*, 2006).

Al-Sahab *et al* (2008) studied breastfeeding behaviour among Muslim and Christian mothers. He reported that Islamic teaching plays a significant role in continuation of

breasfeeding until four months of age with Muslim mothers twice likely to breast-feed compare with Christian women.

2.4.2 Risk of cancer

There are several mechanism postulated for association between breast-feeding and breast cancer. Unsuckled breasts cause milk has a slightly alkaline composition in comparison to that from suckled breasts, which remain acidic during breast-feeding. This alkaline environment will cause epithelial cell to undergo preneoplastic alterations, such as hyperplasia, cell atypia, and increased mitotic activity at a more frequent rate. Cholesterol–b-epoxide level, a potential carcinogen is lower in the breast fluid of women during and up to 2 years after breast-feeding (Lipworth *et al*, 2000).

Lactation causes long-term reduced endogenous estrogen, increased prolactin production and reduce exposure to estrogen thus inhibiting the initiation or growth of breast cancer cells. Excretion of carcinogenic agents from the breast ductal tissue through breast-feeding also been suggested for protective effect of breast cancer (Lipworth *et al*, 2000).

Although the highest prevalence of breastfeeding in Malaysia was in Kelantan but unfortunately this traditional habit of reproduction has been abandon due to urbanisation. Women have postponed marriages or having children and this

reproductive pattern behaviour increasing risk of breast cancer and will increase incidence of breast cancer in Malaysia (Norsa'adah *et al.*, 2005).

2.5 EPIDEMIOLOGY OF BREAST CANCER

All women are at risk of developing breast cancer regardless of their ethnic or country of origin. It is considered as the commonest cancer among women worldwide. The rate of incidence varies. "Rate" refers to number of breast cancer incidence per 100,000 woman-years. The incidence rate of breast cancer is low in Far Eastern and South Eastern Asian countries; intermediate (around 20) in South America and Southern Europe; and the highest (more than 23) in Western Europe and North America (Lacey *et al*, 2002).

A difference in incidence rate among countries indicates the importance of inherent genetic risk in breast cancer etiology or may be due to differential access and utilization of health care resources such as screening and diagnosis (Lacey *et al*, 2002). Recently, the incidence of breast cancer in developing Asian countries is emerging as the commonest female malignancy, overtaking cancer of the uterine cervix (Agarwal *et al*, 2007).

2.5.1 Breast cancer in Asia

In Asia, breast cancer is the leading cause of cancer-related deaths (Agarwal *et al*, 2007). Increasing trend of breast cancer in developing countries is a result of the 'westernisation' of lifestyles such as childbearing, dietary habits and exposure to exogenous estrogen, towards of women in industrialised countries. Bray *et al* (2004) reported the comparisons of breast cancer risk in (low-risk) Asian populations migrating to the (high-risk) United States of America. It showed that environmental (rather than genetic) factors were responsible for most of the observed international and inter-ethnic differences in breast cancer incidence. Apart from that, only about fifty five percent of breast cancer cases can be explained by identified risk factors despite extensive historical and current investigation (Lacey *et al*, 2002).

2.5.2 Breast cancer in Malaysia

In Malaysia, there was lack of data on incidence of breast cancer until the National Cancer Registry (NCR) was started in 2003 (Yip *et al*, 2006). This current data on incidence of cancer only refers to Peninsular Malaysia. There are serious uncertainty about cancer registration from Sabah and Sarawak because inadequate reporting of cases (Lim and Yahya, 2004). Although the incidence of breast cancer here is lower than in the western world, breast cancer is considered as the leading cause of cancer death among Malaysian women (Taib *et al*, 2007).

Age standardised incidence rate (ASR) of breast cancer in Malaysia are 46.2 per 100,000 women. One in twenty women Malaysian woman will develop breast cancer in their lifetime. Statistical incidence of breast cancer in Malaysia in 2003 showed that 50% of patients were below the age of 50 years, with 40-49 year old as the prevalent age group, accounting for more than 30% of the cases (Yip *et al*, 2006).

2.6 RISK FACTORS FOR BREAST CANCER

Table 2.1 Risk Factors for developing breast cancer (Adapted from Yip *et al* , 2006)

Increasing age
Geographic location
Family history
Reproductive factors
Early menarche less than 11 years
Late menopause more than 55 years
Nulliparity
Late first child-birth more than 30 years
Carcinoma of the uterus
Carcinoma of the ovary
Dietary factors – diet rich in animal fats
Exogenous hormones - Oral contraceptives

Table 2.1 (Cont.)

Hormone replacement therapy
Alcohol – more than 2 drinks pre day
Postmenopausal obesity
Higher socio-economic group
Limited breast feeding (for long periods is a protective factor)

Determining the risk factors in breast cancer will offer hopeful promise of modifying those factors. Some of the risk factors of breast cancer can be modified either through behavioural or environmental changes (Norsa'adah *et al.*, 2005). Factors that can influence the risk of breast cancer are old age, (BRCA1/BRCA2) gene mutations, previous diagnosis of atypical ductal or lobular hyperplasia, first-degree relative with a breast cancer, longer exposure to endogenous hormones (early menarche, late menopause and obesity, or with recent and prolonged use of hormone replacement therapy) or with behavioural factors such as high alcohol and fat intake. Risk factors related to lifestyle can be changed (Biglia *et al*, 2004).

Women with BRCA 1 and BRCA 2 mutation carrier have a 37–85% cumulative risk of developing breast cancer before 70 years of age. History of atypical ductal or lobular hyperplasia is associated with a two to fourfold increase in risk of developing breast cancer. Family history of breast cancer is one of important risk factor. Risk of

developing breast cancer is increased by two to three times when there is a strong family history of breast cancer (Biglia *et al* 2004).

Long exposure to endogenous hormones as a result of early menarche, late menopause and obesity, or with recent and prolonged use of hormone replacement therapy (HRT) or with behavioural factors such as high alcohol and high fat intake carries a relative risk between one and two (Biglia *et al* 2004).

The incidence rate of breast cancer of certain races changes among migrants, who rather quickly acquire the rates in their host country, indicate that lifestyle factors can dramatically affect risk of developing breast cancer (Lacey *et al*, 2002). Evidence in migratory study showed increase incidence of breast cancer of certain races when their migrate to countries that their per capita intake of dietary fat is higher (Kamarudin *et al*, 2006). Korean migrants living in the United States have substantially higher incidence levels of breast cancer than women in their mother country. This finding suggests the risk of breast cancer might further increase according to the changes in environmental habits (Yoo *et al*, 2006).

Hormonal concentration are effected by physical activity and exercise, thus they can affect the occurrence of diseases especially chronic diseases such as malignancy. Estrogen hormone exposure that is secreted by the fat tissue can indirectly be reduced by exercise. Exercise can interrupt the menstrual cycle by suppressing the pulsatile release of gonadotrophin-releasing hormone. Reducing the fat tissue will indirectly

reduce breast exposure to the estrogen hormone. In view of above reason, encouragement of healthy lifestyle should be continuous and practiced (Kamarudin *et al*, 2006).

It is important to study the risk factors in breast cancer so that suitable preventive measures can be advise (Kamarudin *et al*, 2006). Incidence of breast cancer can be decrease by the changing in modifiable risk factors such as hormone replacement therapy, alcohol consumption, lack of physical activity and duration of breastfeeding (Baquet *et al*, 2008). Risk of getting breast cancer is increase in certain lifestyle (Kamarudin *et al*, 2006). Study on risk factors in Kelantan showed that the higher risks of breast cancer were significantly associated with nulliparity, overweight/obesity, family history of breast cancer and oral contraceptive usage (Norsa'adah *et al*, 2005).

2.7 RACE AND BREAST CANCER

There are variations in breast carcinoma incidence, mortality, and survival among multiracial/multiethnic populations. Variations in incidence rates of breast cancer among multicultural populations suggest that etiologic factors differ in their biologic expression (Hunter, 2000).

Breast cancer in African American women is biologically more aggressive, with more poorly differentiated tumors, high grade nuclear atypia, and less estrogen receptor positivity compared with White women (Hunter, 2000). Breast cancer has a lower incidence in Asia than in Europe and North America. There are exceptional countries in Asia like Pakistan and the Philippines with relatively high rates, suggesting to major differences in the impact of risk or beneficial factors in the region (Moore *et al*, 2003).

Breast cancer patients among Indonesian, Malaysia and Thailand showed aggressive phenotype (Aryandoyo *et al,* 2006). Depending on racial distribution, the most common incidence of breast cancer in Malaysia is Chinese followed by Indian women and then Malay women (Taib *et al*, 2007).

2.8 AGE AND BREAST CANCER

Young age is an indicator of poor prognosis in breast cancer patients (Agarwal *et al,* 2007). Majority of breast cancers occur in old age with approximately ⅔ breast cancer cases are found after 55 years of age. There are two main breast cancer populations according to age at onset. The first type occurs at early-onset with peak incidence near age 50 years. The second breast cancer type occurs at late-onset with its mode occurring at age 70 years (Anderson *et al*, 2006).

Young breast cancer patients usually presented with more advanced stage disease and have more aggressive tumor characteristics (higher grade tumors and more estrogen- and progesterone receptor-negative tumors) (Maggard *et al* 2003). They usually have a greater chance of having an endocrine-unresponsive tumor, and they are more likely to present with more extensively proliferating and vessel invading disease (Colleoni *et al*,, 2002).

There is a difficulty in detecting tumours in the breasts of young women is because of the density of the mammary glands and this problem is particularly pronounced among pregnant and lactating women (Kroman *et al*, 2000). Study has showed that very young patients less than 35 years old may not benefit from hormone therapy, even in cases of hormone receptor–positive disease (Ahn *et al*, 2007).

Ahn *et al* (2007) reports younger patients with age less than 35 years old showed worse prognosis than older patients (age 35 to 50 years). They had the worst prognosis, with a 1.46-fold increased risk of dying (Kroman *et al*, 2000). Regardless of tumour size or lymph nodes status, young breast cancer patients have a greater probability of death than the older patients (Ahn *et al*, 2007). The poor survival rate seen in young women may reflect differences in tumor biology (Chung *et al*, 1996).

2.9 LATERALITY OF BREAST CANCER

Breast cancer is more likely to be diagnosed in the left breast than the right. It was five to seven percent more common in the left than in the right breast (Perkins *et al*, 2004; Ekbom *et al*, 1994). This finding that was generally consistent among age, race, ethnicity, gender, stage, and histologic categories but the reasons are still uncertain (Perkins *et al*, 2004).

Various hypotheses have been proposed but have not been uniformly accepted or confirmed (Perkins *et al*, 2004). Study by Ekbom *et al* (1994) on a very huge number of women breast cancer over a period of 20 years of Swedish Cancer Registry. He made conclusion in his study; (i) that the higher frequency of cancer on the left rather than the right breast is not limited to invasive disease but also relevant to pre-invasive (in situ) cancer; (ii) that a similar laterality pattern for male as for female breast cancer.

2.10 TUMOUR SIZE (TUMOUR DIAMETER)

Tumour size is an important indicator in breast cancer. The importance of tumor size is shown in the TNM Staging System. There are several methods to determine tumour size either by clinical palpation, breast imaging studies or direct measurement from the surgical resection specimen. The pathology measurement is considered to be a gold standard in tumour size measurement (Pritt *et al*, 2005).

Tumour size is based on the maximum tumour dimension although tumour volume is a better measurement of an individual's tumour burden. Maximum tumour dimension is easier to assess and more practical to apply than tumour volume. Following surgery, the tumour size will be measured in three directions including the longest axis and two orthogonal axes and only the longest axis is taken for staging purposes. The measurement should be accurate since the difference of a single millimeter will change categorical staging classification. This improper classification will alter patient's management (Pritt, *et al,* 2005).

2.10.1 TNM staging

Based on the greatest dimension, the tumour size will be categorized into T1, T2, T3 and T4. Tumour size measures 2 cm or less is T1 lesion. T1 is further subcategorized into T1 mic, T1a, T1b, T1c. T1 mic cancer is when there is present of micro invasion measuring 0.1 cm or less in the greatest dimension. T1a, T1b, and T1c measure 0.1 to 0.5 cm, 0.5 to 1 cm, and 1 to 2 cm, respectively. A T2 tumor is more than 2 cm and less than 5 cm and T3 is tumors more than 5 cm in the greatest dimension. Tumour of any size but has a direct extension to the skin or to the chest wall is classified under T4 tumour. T4 is further subcategorized into T4a, T4b, T4c and T4d. T4a tumors extend to the chest wall, not including the pectoralis muscle. T4b breast cancers show edema, including peau d'orange, skin ulceration, or satellite skin nodules in ipsilateral breast and T4c tumor is a combination of T4 a and T4b. Inflammatory carcinoma is classified as T4d (Whitman *et al*, 2006).