ASSOCIATIONS BETWEEN DIETARY, LIFESTYLE BEHAVIOURAL PRACTICES AND QUALITY OF LIFE AMONG MALAY SURVIVORS OF BREAST CANCER IN KELANTAN

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By

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ABSTRAK

Pemahaman amalan pemakanan dan gaya hidup dalam kalangan survivor kanser payudara adalah amat penting untuk meningkatkan kesihatan dan kesejahteraan, dan kualiti kehidupan mereka. Walau bagaimanapun, kajian tentang kesan amalan pemakanan dan gaya hidup selepas diagnosis kanser payudaru amat kurang. Tujuan utama kajian ini dilakukan adalah untuk menentukan amalan pemakanan dan gaya hidup serta kesannya terhadap kualiti kehidupan dalam kalangan survivor kanser payudara. Seramai 92 survivor kanser payudara di Kelantan telah menyertai kajian ini. Beberapa protokol penilaian telah dijalankan seperti borang soal selidik yang telah diujipakai mengenai sosiodemografi, amalan pemakanan, dan gaya hidup peserta, manakala kualiti kehidupan (QoL) dinilai dengan menggunakan EORTC QLQ-C30 dan modul kanser payudara BR23 dalam versi Bahasa Malaysia. Pengambilan nutrien oleh peserta telah dinilai dengan menggunakan semi-kuantitatif borang kekerapan makanan (FFQ) yang mengandungi 15 kumpulan makanan biasa dimakan oleh orang Kelantan. Purata umur peserta adalah 49.8 ± 8.1, dengan purata indeks jism badan (BMI) 26.2 ± 4.9. Lebih daripada separuh peserta (53.2%) diklasifikasikan sebagai risiko berlebihan berat badan dan obes. Amalan pemakanan selepas diagnosis kanser payudara menunjukkan bahawa majoriti peserta (65.2%) the mengambil makanan ringan sekurang-kurangnya satu kali dalam sehari dan majoriti mereka menyediakan makanan dengan kaedah menggoreng (62.0%). Dari segi amalan membaca label pemakanan, penggunaan label pemakanan dalam kalangan peserta adalah rendah, di mana majoriti tidak pernah atau jarang membaca label nutrisi yang terkandung dalam makanan pembungkusan. Tempoh median masa digunakan untuk aktiviti lasak oleh

peserta hanya 0.3 jam/hari [CIS 95%: 0,3-0,6], di mana 0.5 jam/hari [CIS 95%: 0,4-0,7] telah digunakan untuk aktiviti ringan. Analisis tentang akitiviti fizikal (PA) dan amalan akitiviti sedentari menunjukkan bahawa dua per tiga daripada peserta (69.6%) telah melibat dalam PA sederhana dengan hanya 28.3% daripada meraka mengamal akitiviti fizikal aktif. Analisis korelasi Pearson menunjukkan terdapat perbezaan yang signifikan di antara BMI dengan sub skala nilai QoL fungsi fizikal ($r = -0,336$; $p < 0.01$) dan imej badan yang lebih rendah ($r = -0,237$; $p < 0.05$). Analisis selanjutnya telah dijalankan untuk menentukan perbezaan profil nutrien status survival daripada kanser payudara dan didapati bahawa terdapat perbezaan yang signifikan dalam pengambilan nutrien protein diet antara tahun survival daripada kanser payudara, di mana peserta yang hidup ≥ 5 tahun daripada kanser payudara mempunyai lebih tinggi dalam protein diet ($p < 0.005$), karbohidrat ($p < 0.05$), tenaga ($p < 0.05$), ($p < 0.05$), jumlah serat ($p < 0.05$), lemak penting seperti Omega-6 FA, jumlah asid lemak ($p < 0.05$), kalsium ($p < 0.005$), besi ($p < 0.05$), dan vitamin C ($p < 0.05$) berbanding dengan mereka yang hidup <5 tahun.. Kesimpulannya, walaupun telah disahkan menghidap kanser payudara, majoriti peserta ini masih mengamalkan amalan pemakanan dan gaya hidup yang tidak sihat, dengan majoriti daripada mereka lebih suka mengambil makanan yang tinggi lemak, dan kesedaran tentang pemakanan seperti penggunaan label nutrisi makanan masih rendah. Usaha dan strategi pemakanan yang sihat dan amalan gaya hidup aktif perlu digalakkan dalam kalangan survivor kanser payudara bagi mengekalkan kesihatan optima populasi ini.

ABSTRACT

Understanding the dietary and lifestyle practices among survivors of breast cancer are important in order to improve the general health and wellbeing, and quality of life. However, little is known about the effects of diet and lifestyle practices after diagnosis on breast cancer survival. Therefore, the main aim of the present study was to determine the dietary and lifestyle practices and its impact on the quality of life among 92 Malay survivors of breast cancer living in Kelantan. Pre-piloted questionnaire was used to assess the socio-economic status, dietary and lifestyle-related behavioural practices, whereas quality of life (QoL) of the participants were assessed using validated Malay-version of the the EORTC QLQ-C30 and its breast cancer module BR23. Nutrient intake of the participants was assessed using semi-quantitative food frequency questionnaire (FFQ) of 15 food groups commonly consumed foods in Kelantan. The mean age of the participants were 49.8 ± 8.1, with the mean body mass index (BMI) of 26.2 ± 4.9. More than half of them (53.2%) were classified as overweight and obese. Dietary practices after diagnosis of cancer showed that majority of the participants (65.2%) were generally consumed snacks at least once in a day and majority were preferred to consume food prepared in frying method (62.0%). The use of nutrition food label among these participants was low, whereby majority of the participants were never or rarely read the nutrition label contained in foods packaging. The median duration of time spent on vigorous activity by the participants was only 0.3 hours/day [95 % CIs: 0.3-0.6], where 0.5 hours/day [95 % CIs: 0.4-0.7] was spent on light activity. Analysis of habitual physical activity (PA) and sedentary-based activity practices showed that almost two-thirds of the participants (69.6%)

were engaged in moderate PA levels with only 28.3% of them were physically active. *Pearson* correlation analysis showed there was significant difference between BMI with QOL subscales of physical functioning (r=-0.336; p<0.01) and lower body image (r=-0.237; p<0.05). Further analysis was conducted to examine the differences between nutrients profile and survival status among these participants, it showed that there was a significant difference in essential nutrients intake between breast cancer survival years, in which participants with higher survival status of ≥ 5 had significantly higher intake of dietary protein (p<0.005), carbohydrate (p<0.05), calories (p<0.05), total fiber (p<0.05), essential omega-6 fatty acids (p<0.05), calcium (p<0.005), iron (p<0.05) and vitamin C (p<0.05) compared with those with shorter survival years of less than 5 y. In conclusion, majority of these participants were still practicing unhealthy dietary and lifestyle practices, despite being diagnosed with breast cancer. Majority of them were preferred to consume foods high in fat, and nutrition concern such as the use of nutrition label of packaged food consumed among them was also low. Continuous efforts and strategies of healthy eating and active lifestyle practices should be promoted among survivor of cancers in order to maintain optimal health and general well-being of these populations.

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LIST OF ABBREVIATIONS

ACS	American Cancer Society
ASR	Age-standardized incidence rate
BMI	Body mass index
DCIS	Ductal carcinoma in situ
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
HER	Human epidermal growth factor receptor
HR	Hazard ratio
LCIS	Lobular carcinoma in situ
MET	Metabolic equivalent
NCCS	National Coalition of Cancer Survivorship
PA	Physical activity
QoL	Quality of life
RNI	Recommended Nutrient Intake
SD	Standard deviation
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.0 Background of study

Breast cancer (BC) is defined as cancer that forms in the tissues of the breast. The most common type of breast cancer is ductal carcinoma in situ (DCIS). DCIS begins in the lining of the milk ducts. It accounts for 70% of invasive breast cancer. Another type of breast cancer is lobular carcinoma in situ (LCIS), which begins in the milk glands of the breast. Invasive breast cancer is breast cancer that has spread outside the membrane of the duct or lobule into the breast tissue. It is then possible to spread into lymph nodes in the armpit or beyond. Breast cancer can be categorized in stages, which is stage 0 (carcinoma in situ), stage I (IA, IB), stage II (IIA, IIB), stage IIIA, stage IIIB, stage IIIC, and stage IV.

Breast cancer is ranked as the second most common cancer in the world while ranked the top among women cancer (Ferlay *et al.*, 2014). The incidence of breast cancer is increasing at an alarming rate. For instance, approximately 1.67 million women were diagnosed with breast cancer in 2012 and there were 6.3 million women alive who had been diagnosed with breast cancer in the previous five years **(Table 1.1)**. Since 2008, the incidence of breast cancer has increased dramatically by more than 20%, while the mortality has increased by 14% (Ferlay *et al.*, 2014). The total number of patients who had been diagnosed with breast cancer up to one year, three years, and five years are increasing drastically as well. Worldwide, the 5-year prevalence for

Table 1.1: Estimated new breast cancer cases (thousands)

	Female			
	Cases	(%)	ASR (world) †	Cum. risk Ω
Breast cancer	1677	25.2	43.4	4.6

†ASR per 100,000
ΩCumulative risks to age 75 years (percent)

(Source: Ferlay *et al.*, 2014)

Table 1.2: Estimated incidence and prevalence of breast cancer of females in worldwide and in Malaysia 2012

	Incidence	**Prevalence**		
		1-year (prop.)	**3-year (prop.)**	**5-year (prop.)**
Worldwide	1676332	1466527 (56.5)	4035526 (155.3)	6255391 (240.8)
Malaysia	5410	4691 (45.7)	12470 (121.5)	18928 (184.4)

(Source: Ferlay *et al.*, 2014 and Bray et al., 2013)

breast cancer is 6255391, while in Malaysia, it is 18928 **(Table 1.2)** (Bray *et al.*, 2013). The advancement in the technology of early detection and effective treatment has caused the breast cancer survival rate to grow significantly, thus creating a relatively large population of survivors of breast cancer.

The working definition of a cancer survivor has changed over time, and there has been inconsistency in the use of the term (Khan *et al.*, 2012). Before 1986, the term cancer "survivor" was generally restricted to someone living cancer free for five or more years (Feuerstein, 2007). On the other hand, the National Coalition of Cancer Survivorship expanded the definition of "survivor" to include anyone with cancer

"from the time of diagnosis, through the balance of his or her life" (Leigh & Logan, 1991; NCCS, 1995). Since then, many researchers have offered additional definitions of survivors, some of which include family members, friends, and caregivers (Aziz & Rowland, 2003; Feuerstein, 2007; Kelly *et al.*, 2011; Twombly, 2004). The operational definition of survivors of breast cancer for this study is those who survived for equal or more than one year after completion of cancer treatment.

The cancer care continuum has been used since the mid-1970s to describe various points in cancer life. It helps to describe various points from cancer prevention, early detection, diagnosis, treatment, survivorship, and end of life. Survivors are now large and growing populations; therefore, survivorship has been added to the continuum. **Figure 1.1** shows the cancer care continuum.

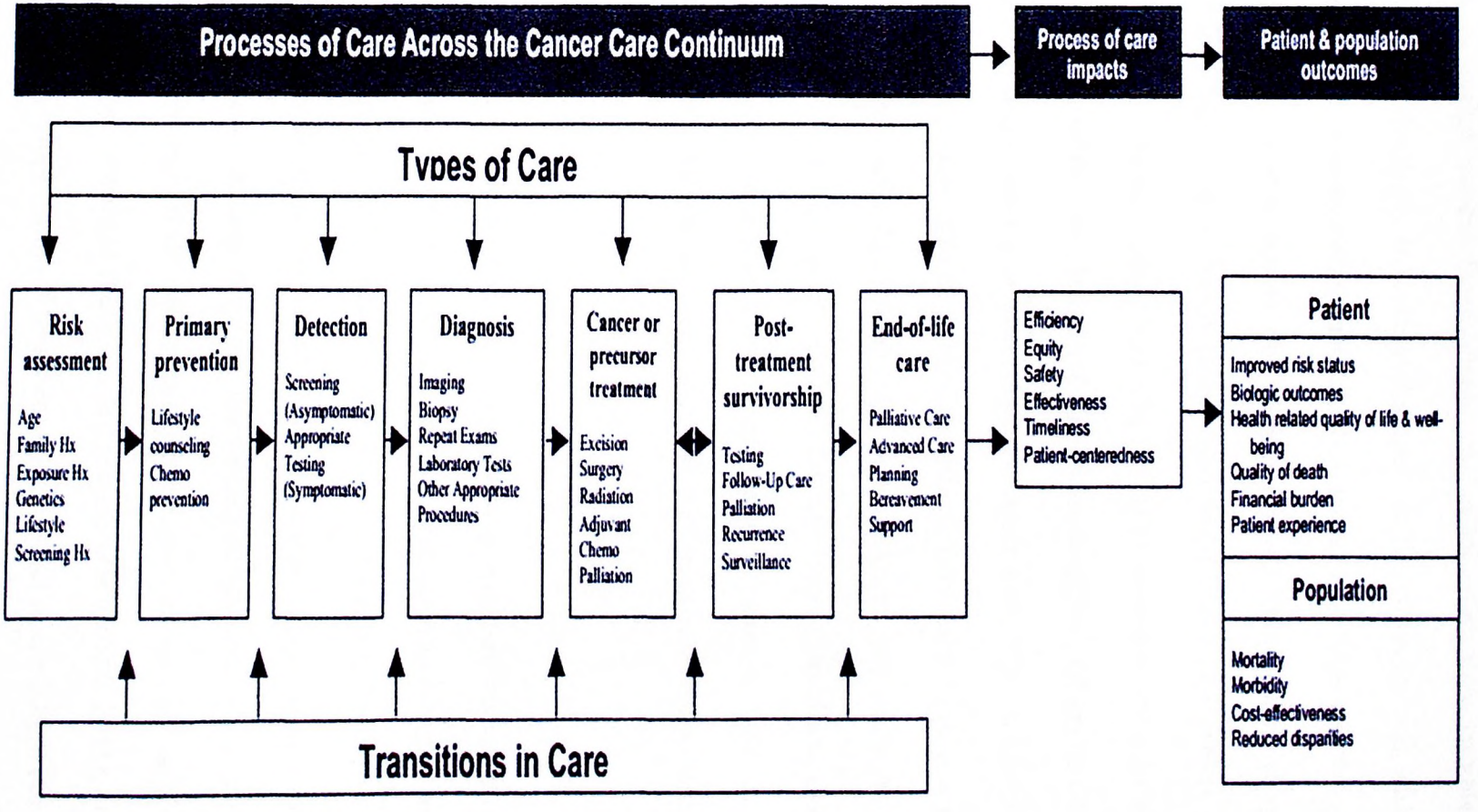

Figure 1.1: Cancer Care Continuum

(Source: National Cancer Institute,1995)

Survivors of breast cancer faced plenty challenges after they completed their treatment. One of the major concerns is that they are fear of recurrence, which is also known as second primary breast cancer. They have much high risk to get a new breast cancer compared to people who have never had breast cancer (Raymond & Hogue, 2006). Survivors of breast cancer also faced some late effects of breast cancer treatment. Although most of the side effects of treatment are dismissed when the treatment completed, there may have some long-term side effects or other health effects that can occur months or years after treatment ends. This is hard to make a plan for cope with these effects as the late effects may vary from one person to another. Some common late effects of breast cancer are early menopause, menopausal symptoms such as hot flashes, fertility issues, emotional distress and depression, sexuality and intimacy issues, fatigue, and insomnia. This consequently could affect to the quality of life and survivorship of those affected patients (Knobf, 2007).

Patient with cancer at later stage may have already experienced weight loss and cachexia. The untreated side effects of cancer treatment, such as vomiting and nausea would consequently result in excessive weight loss. Therefore, in the past, cancer was considered as a disease associated with weight loss. However, now most of the patients are diagnosed at early stage and the treatments have become more effective. This had led to growing number of patients who they are overweight or obese at the beginning of cancer treatment (Pekmezi & Demark-Wahnefried, 2011), and weight gain is a frequent complication of treatment (Chlebowski *et al.*, 2006). For example, the late effects of radiation therapy are lymphedema and changes in look and feel of the breast, while the weight gain are the late effects of chemotherapy. Convincing

data exist that obesity is associated with an increased risk of breast cancer recurrence (Patterson *et al.*, 2010; Protani *et al.*, 2010). Depending on the type of cancer and stage at diagnosis, cancer cause significant metabolic and physiological alterations that can affect the nutrient requirements for both macro and micronutrients.

Nutritional needs of survivors of cancer require changes over the course of survivorship. Therefore, more attentions is particularly needed to support the needs of breast cancer patients in the transition period between end of treatment and survivorship and improve their quality of life. In fact, the portion of cancer survivor expressing their unmet needs is highest in the post-treatment phase when compare to other phases in the cancer continuum (Harrison *et al.*, 2009). The need for informed lifestyle choice for cancer survivors becomes particularly important as they look forward to the successful completion of therapy and seek self-care strategies to improve their long-term outcomes. For many long-term cancer survivors, healthy weight management, healthy diet, physically active lifestyle aimed at preventing recurrence, second primary cancers, and other chronic diseases should be a priority in order to promote overall health, quality of life, and longevity (Coward, 2006).

More than 60% of the world's total cases occur in Africa, Asia, and Central and South America, and these regions account for about 70% of the world's cancer deaths. Asia countries account for 48.0% of the world's total cases (Ferlay *et al.*, 2014). Moreover, the 1-year, 3-year and 5-year prevalence of breast cancer in the Asia region remain the highest among all cancers (Bray *et al.*, 2013). In Asia, there are numerous studies reporting the dietary and behavioral practices of breast cancer patients, as well as for survivors of breast cancer, but merely few studies reporting

the casual association between these factors and quality of life of survivors of breast cancer. In addition, there is no research done on the sedentary lifestyle behaviors in relationship with the quality of life of survivors of breast cancer. Thus, it is of concern to understand the dietary practices and other factors related to the quality of life of survivors of breast cancer. This study is therefore carried out to assess the associations of dietary and lifestyle behavioural practices and quality of life of survivors of breast cancer in Kelantan.

1.1 Problem statement

Breast cancer is ranked as the second most common cancer worldwide that has been received greater attention (Ferlay *et al.*, 2014) **(Figure 1.2)**. Based on the Globocan project done by Ferlay and his colleagues (2014), it was estimated that about 1.67 million women were diagnosed with breast cancer in 2012 **(Figure 1.3)** and approximately 6.3 million women were still alive after being diagnosed with breast cancer in the previous five years. Since 2008, the prevalence of breast cancer has been increased dramatically by 20%, with mortality rate has increased by 14%. It is generally agreed that breast cancer is the most common causes of cancer mortality among women, in which most women were come from developed countries than that of those from developed countries. It was estimated that about 14.3% of total mortality of breast cancer was among women from less developed countries are suffered compared to other developed countries (Ferlay *et al.*, 2014).

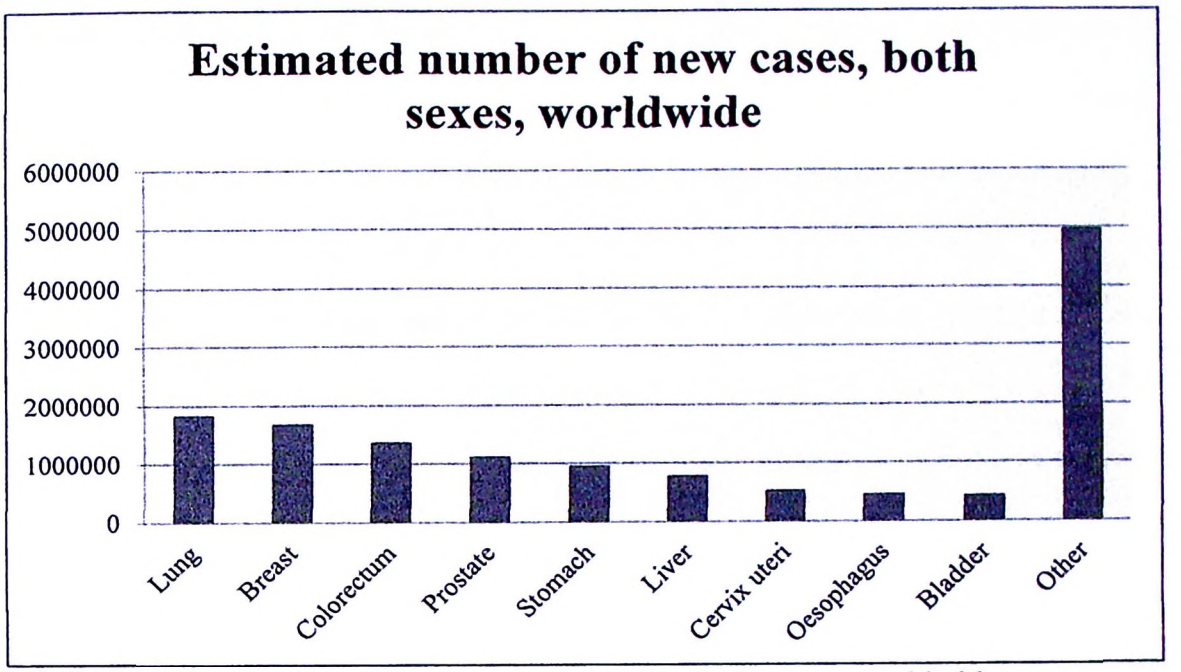

Figure 1.2: Estimated number of new cases among both sexes, worldwide

(Source: Ferlay *et al.*, 2014)

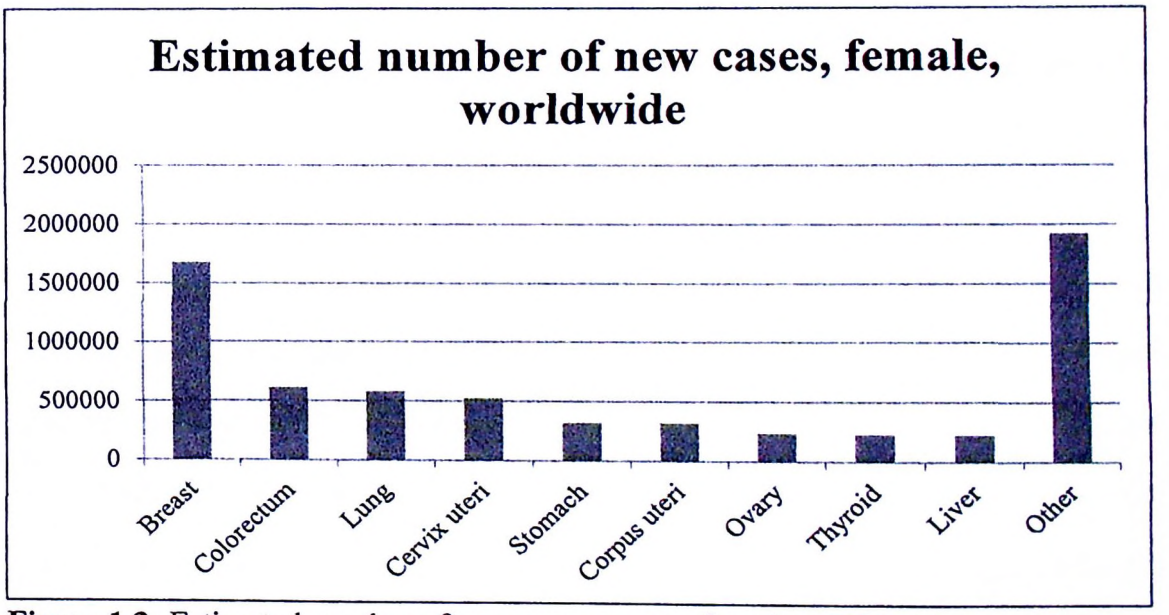

Figure 1.3: Estimated number of new cases among female, worldwide

(Source: Ferlay *et al.*, 2014)

Breast cancer is one of the ten leading cancers among population of Malaysia in 2007 as well as the most frequent cancer among Malaysia females. It contributes 18.1% among all cancers in all residence, 32.1% among Malaysia females. In 2007, 3242 new cases of breast cancer were reported to the NCR of Malaysia, giving an age-standardized incidence rate (ASR) of 29.1 per 100,000 women (Omar & Tamin, 2011). In 2013, 5410 new cases of breast cancer were reported, which increased 67% as compared to year 2007 (Ferlay *et al.*, 2014). It is estimated to increase to 6016 new cases in year 2015.

According to the National Cancer Registry Report, Malaysia, the incidence of breast cancer was highest among Chinese where the ASR was 38.1 per 100,000 population followed by Indian and Malay with the ASR of 33.7 per 100,000 population and 25.4per 100,000 populations respectively. Despite the low ASR rate among Malay population, it showed relatively lowest overall survival rate (Abdullah *et al.*, 2013). This is due to that Malays tend to present at the advanced stage of the cancer as compared to other ethnic group (Hisham & Yip, 2003)

The increasing breast cancer cases have become a great concern and therefore much more attentions are given to breast cancer. Diagnosis of cancer regardless of stage can be stressful as it impacts multiple sphere of life, disrupting physical status, emotional and spiritual well-being and personal relationships for the patient and family (Mukwato *et al.*, 2010). It gives negative impact on the emotional health not only on the patients, but also their families, and caregivers. They faced some degree of depression, anxiety, and fear when cancer becomes part of their lives (Edwards & Clarke, 2004). Moreover, they might feel the loss of control over life events, and

have to deal with changes in body image. Family member and caregivers faced physical demand for practical care giving, emotional strain, change in role and responsibilities, and adjustment to work and career schedules (Mukwato *et al.*, 2010). In addition, survivors of breast cancer are also facing nutritional and lifestyle-related problems. After completing cancer treatment, many symptoms and side effects of treatment that have affected nutritional and physical well-being begin to resolve. However, some of the side-effects persist. In addition, latent effects of treatments may appear for months or years after treatment has been completed (Ewertz & Jensen, 2011; Sunga *et al.*, 2005). Examples of complications of cancer treatment related to nutritional status are persisting fatigue, peripheral neuropathy, changed sense of taste, difficulty chewing and swallowing, difficulty in replenishing lean body mass after the completion of therapy, and persistent bowel changes such as diarrhoea or constipation. Therefore, survivors may require ongoing nutritional assessment and guidance in this phase of survival, which helps to relieve symptoms and stimulate appetite that aid in recovery process.

1.2 Significance of the study

Based on the report of Ferlay and his co-workers (2014), there was a significant increase in the number of cancer cases worldwide from 2008 to 2012, which it increased about 13% in 2012 compared to 2008. It is estimated to increase to another 8.1% in the year 2015 (Ferlay *et al.*, 2014). Breast cancer is the second most common cancer worldwide and the prevalence has been increasing dramatically too to about 20%, with 14% increment in mortality rate (Ferlay *et al.*, 2014). Breast cancer is the top cancer death cause in Malaysia. It is estimated to increase to 6016

new cases in year 2015 and 6977 new cases in 2020. Moreover, the mortality rate is going to increase to from 2572 cases to 2876 cases in 2015, and 3386 in year 2020 (Ferlay *et al.*, 2014).

Despite the increasing incidence rate, technological advances in cancer therapy led to improve cancer outcomes such as survival rate, treatment outcomes, and toxicity (Boini *et al.*, 2004). The quality of life of cancer patients after completing treatment is a major concern. Weight management, dietary patterns and physical activity is given priority in preventing risk of cancer recurrence, the development of second primary cancers, and other related chronic diseases. There are increasing evidence indicates that being overweight increases the risk of recurrence and reduces the likelihood of disease-free and overall survival among those diagnosed with cancer (Patterson *et al.*, 2010; Protani *et al.*, 2010; Vrieling & Kampman, 2010).

Although currently there is limited evidence support the hypothesis that post-treatment intentional weight loss in cancer survivors will result in improved prognosis and overall survival (Protani *et al.*, 2010), results of the Women's Intervention Nutritional Study (WINS) found that a 6-pound weight loss (approximately 4% of initial weight) by taking low-fat diet, reduced the risk of recurrence among postmenopausal survivors of breast cancer, especially those with ER-negative tumours (Chlebowski *et al.*, 2006). However, this clinical trial results are confounded by the impact of a low-fat diet that was the focus of the intervention. Nonetheless, it is hypothesized that improvements in cancer-related outcomes are possible through intentional weight loss in overweight or obese cancer survivors (Miller & Kral, 2008).

In many studies, active lifestyle such as exercise improves quality of life, fatigue, depression, psychosocial distress, and self-esteem. For example, in one randomized controlled trial of survivors of breast cancer, women assigned to moderate intensity resistance and impact training experienced improvements in bone mass and lean muscle mass (Winters-Stone *et al.*, 2011). In another meta-analysis of 44 studies that included over 3000 participants with varying cancer types, cancer survivors randomized to an exercise intervention had significantly reduced cancer-related fatigue levels, with evidence of a linear relationship to the intensity of resistance exercise (Brown *et al.*, 2011). Despite many benefits of being physically active, there are some particular issues that may affect the ability of survivors to perform exercise. The effects of treatments may increase the risk of exercise-related injuries and adverse effects. Moreover, based on current evidence, there are only about 20% to 30% of cancer survivors will be active after they recover from treatments (Pinto & Ciccolo, 2011).

In recent reviews, results from observational studies suggest that diet may affect risk of recurrence, and overall survival in individuals who have been treated for cancer (Norman *et al.*, 2007; Rock & Demark-Wahnefried, 2002). There is a 43% reduction in overall mortality observed in a study of survivors of breast cancer in association with a dietary pattern which is high in vegetables and whole grains (Kwan *et al.*, 2009). Survivors of breast cancer who reported eating at least 5 servings of vegetables and fruits each day and having weekly physical activity equivalent to 30 minutes of walking for 6 days per week were observed to have a higher survival rate. However, there is no significant survival advantage observed for either of these behaviours alone (Pierce *et al.*, 2007).

However, most of these studies are done in the developed countries. There are little studies done in developing countries such as Malaysia pertaining the association between dietary factors, physical activity level and quality of life in survivors of breast cancer. Due to the fact that the Malay survivors of breast cancer has the lowest survival rate in Malaysia (Abdullah *et al.*, 2013), therefore it is important to investigate the modifiable lifestyle behaviours that affect the quality of life of Malay survivors of breast cancer in Kelantan. This can help cancer care professionals to identify the relationship between these factors, and health promotion program or intervention can be carry out to promote the overall well-being of survivors of breast cancer.

1.3 Research Objectives

1.3.1 General Objective

To assess nutritional status, dietary and lifestyle behavioural practices and quality of life in survivors of breast cancer in Kelantan

1.3.2 Specific Objectives

i. To assess the dietary practices of survivors of breast cancer in Kelantan

ii. To assess the lifestyle behavioural practices of survivors of breast cancer in Kelantan

iii. To determine the quality of life of survivors of breast cancer in Kelantan

iv. To determine if there is an association between dietary practices and quality of life of survivors of breast cancer in Kelantan

v. To determine if there is an association between lifestyle behavioural practices and quality of life of survivors of breast cancer in Kelantan

1.4 Research Hypotheses

1.4.1 Null Hypothesis

i. There is no significant association between dietary practices and quality of life among survivors of breast cancer in Kelantan

ii. There is no significant association between physical activity level and quality of life among survivors of breast cancer in Kelantan

1.4.2 Alternative Hypothesis

i. There is significant association between dietary practices and quality of life among survivors of breast cancer in Kelantan

ii. There is significant association between physical activity level and quality of life among survivors of breast cancer in Kelantan

1.5 Research Questions

i. How is the dietary practice of survivors of breast cancer in Kelantan?

ii. What is the dietary intake of survivors of breast cancer in Kelantan?

iii. What is the physical activity level of survivors of breast cancer in Kelantan?

iv. What is the quality of life of survivors of breast cancer in Kelantan?

v. What is the association between dietary intake and quality of life of survivors of breast cancer in Kelantan?

vi. What is the association between dietary practices and quality of life of survivors of breast cancer in Kelantan?

vii. What is the association between physical activity level and quality of life of survivors of breast cancer in Kelantan?

1.6 Conceptual Framework

Quality of life of survivors of breast cancer is affected by complicated multifactorial factors In this study, the main focus are on dietary intakes and practices, as well as lifestyle practices of participants, taking into account of possible confounding factors such as early life status, menopausal status, nutritional status, educational level, occupation, parity, age, as well as household income **(Figure 1.4)**.

Dietary behavioral practices of the participants were assessed by several dietary habits intakes such as daily breakfast, lunch, dinner, snacking, and fruits and vegetables. Lifestyle practices such as engagement of daily sport-related activities and sedentary-based practice such as weekly television watching and electronic games playing, were also gathered in the study.

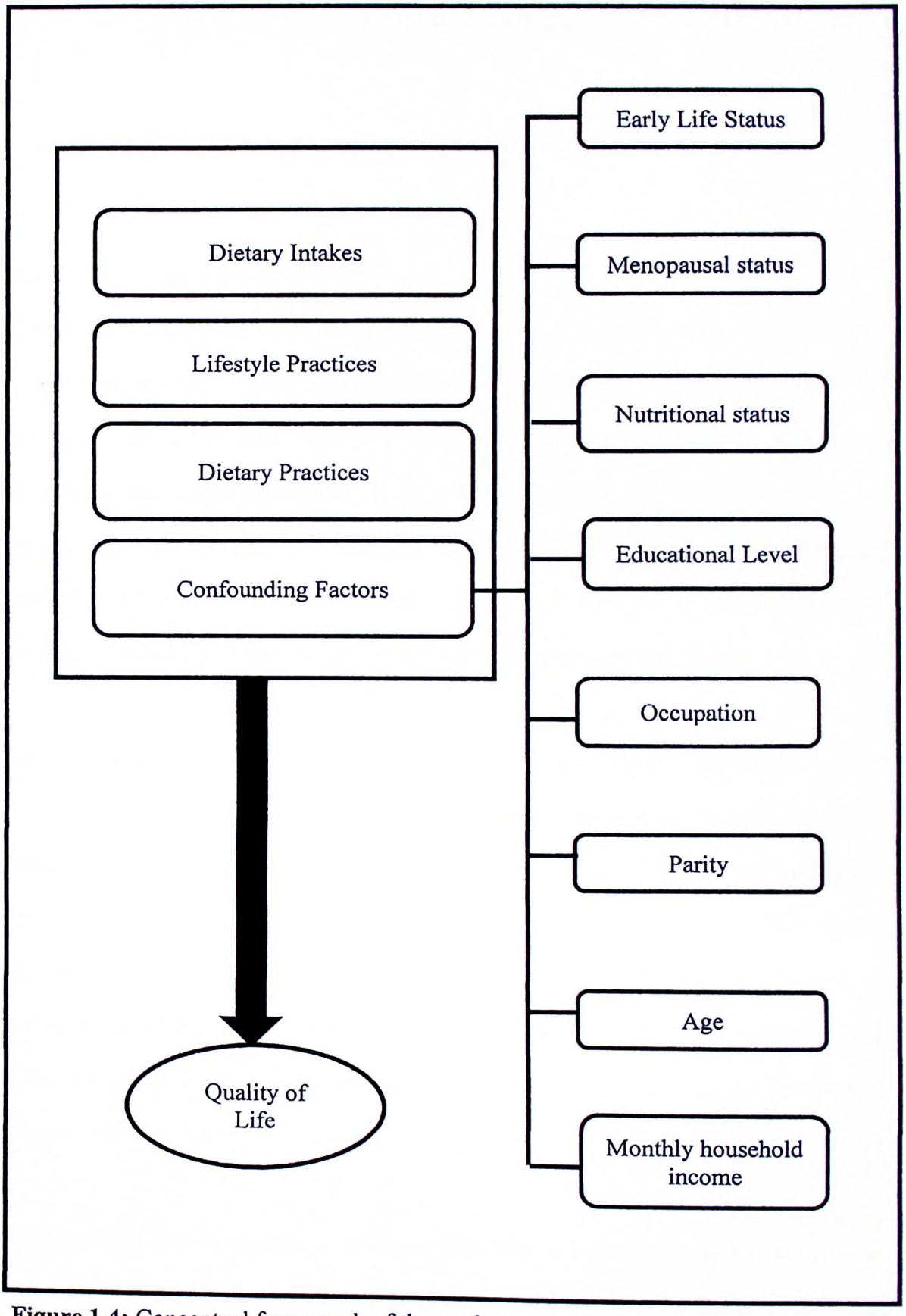

Figure 1.4: Conceptual framework of the study

CHAPTER TWO

LITERATURE REVIEW

2.0 Overview of breast cancer

There are 3 types of breast carcinoma in situ (stage 0), which is DCIS, LCIS, and paget disease of the nipple. Paget disease of the nipple is a condition in which the abnormal cells are found in the nipple only (American Cancer Society, 2014). Stage I is divided into stages IA and IB. In stage IA, the tumour is 2 centimetres (cm) or smaller, and has not spread outside the breast. In stage IB, small clusters of breast cancer cells are found in the lymph nodes and either there is no tumour found in the breast or the tumour is 2cm or smaller (American Cancer Society, 2014).

Stage II is also divided into (a) stage IIA: no tumour found in the breast or the tumour is 2cm or smaller. Cancer (larger than 2mm) is found in 1 to 3 axillary lymph nodes or lymph nodes near the breastbone, or the tumour is >2cm but <5cm, and it has not spread to lymph nodes, (b) stage IIB: the tumour is >2cm but <5cm, small clusters of breast cancer cells (>0.2mm but <2mm) are found in the lymph nodes; or >2cm but <5cm, cancer has spread to 1 to 3 axillary lymph nodes or lymph nodes near the breastbone; or >5cm and has not spread to the lymph nodes (American Cancer Society, 2014).

In stage IIIA, there is no tumour found in the breast or the tumour can be vary in size. Cancer is found in 4 to 9 axillary lymph nodes or lymph nodes near the breastbone; or the tumour is >5cm, small clusters of breast cancer cells (>0.2mm but <2mm) are

found in the lymph nodes; or the tumour is >5cm, and the cancer has spread to 1 to 3 axillary lymph nodes or lymph nodes near the breastbone. The tumour in stage IIIB may be in any size and the cancer has spread to the chest wall or to the skin of the breast or both. It causes swelling or ulcer. The cancer may have spread to up to 9 axillary lymph nodes or the lymph nodes near the breastbone. In stage IIIC, no tumour is found in the breast or the tumour may be in any size, spread to the skin of breast and causes swelling or ulcer, has spread to the chest wall. The cancer in stage IIIC has spread to 10 or more axillary lymph nodes, or lymph nodes above or below the collarbone, or axillary lymph nodes and lymph nodes near the breastbone (American Cancer Society, 2014).

Stage IV, is also known as metastasis breast cancer. The cancer has spread to other organs of the body, usually the bones, lungs, liver, or brain (American Cancer Society, 2014).

2.1 Pathogenesis of breast cancer development

Breast cancer pathogenesis may be driven by activation of steroid hormone receptor like estrogen and progesterone and may also be driven by receptor tyrosine kinase. About 25% of breast cancers are termed HER2-positive because cells expressed HER2 at high level. Patients with cells do not overexpress HER2 are said to be HER2-negative. These two types of breast cancer may different in pathogenesis and prognosis. HER2 is the member of EGFR family receptor tyrosine kinase which also include EGFR, HER2, HER3 and HER4. Once activated, these receptors induced downstream signaling to homodimerization or crosstalk through heterodimerization.

EGFR is often overexpressed in primary breast tumor. As a result of inappropriate activation of EGFR and dysregulation of downstream signaling pathways can occur. EGFR overexpression is a negative prognostic factor in breast cancer and is often associated with advancement of the disease. EGFR-HER2 dimers may be associated with the metastatic potential of a breast cancer. EGFR overexpression is also correlated with resistance to endocrine therapy in ER-positive breast tumors. EGFR overexpression is correlated with decreased survival in patients with breast cancer treat with anthracyclin-based chemotherapy (Ganeberg *et al.*, 2000). HER2 is overexpressed in approximately 25% of breast cancer while HER2 is unique it does not bind with specific ligand. It can be activated by homodimerization or heterodimerization with other EGFR family members. HER2-HER3 dimers provided strong mitogenic signals to proliferating cells. HER2 overexpression and dysregulated HER2 signaling are associated with the aggressive of the disease and the known negative prognostic factors in breast cancer (Ganeberg *et al.*, 2000). HER2 is also a validated target for breast cancer therapy. HER3 overexpression is correlated with shorter disease pre-survival in breast cancer because HER3 lacks intrinsic tyrosine kinase activity. It can only initiate signal transduction when dimerized with other EGFR family members. HER2 is a preferred heterodimerization partner for HER3. HER2-HER3 heterodimers provided strong mitogenic signal to proliferating cells. The HER2-HER3 dimer paired can activate multiple downstream targets including the PI3K/AKT pathway, a signaling cascade critical for tumorigenesis. HER4 can dimerized with all members of EGFR family. Interaction of HER4 with various ligands and EGFR family members activated several downstream signaling pathways. In breast cancer, HER4 may become overexpressed. HER4 overexpression may be a negative prognostic marker in breast cancer.

However, more data are needed to understand the role of HER4 in the pathogenesis of breast cancer (Gancberg *et al.*, 2000).

2.2 Epidemiology of breast cancer

Breast cancer is ranked as the second most common cancer among females. The incidence of breast cancer is increasing at an alarming rate. In 2012, 1.67 million women were diagnosed with breast cancer and there were 6.3 million women alive who had been diagnosed with breast cancer in the previous five years. In Malaysia, it contributes 28.0% among female in year 2012. It is reported that breast cancer is common among females of Malay origins (1432 new cases), followed by Chinese and Indian, which is 1343 and 297 new cases respectively **(Table 2.2).** Furthermore, breast cancer is one of the five most common cancers has been reported among females in Kelantan (Omar *et al.*, 2011).

According to Surveillance, Epidemiology, and End Results Program (SEER), the relative survival of those who survived 5 years or more after being diagnosed with breast cancer is 89.2%. Stage at diagnosis is also affecting the survivorship rates for new breast cancer cases have been stable over the last 10 years. Death rates have been falling on average 1.9% each year over 2002-2011 (Howlader *et al.*, 2015).

Table 2.1: All cancers exclude non-melanoma skin cancer - Estimated incidence, all ages: female

	No. of cases	Crude rate	ASR (World)	Cum. risk
Malaysia	19301	133.0	134.6	14.43

Crude and age-standardized rates per 100,000.
Cumulative risk [0-74 years in percentage (%)]

(Source: Ferlay *et al.*, 2014)

Table 2.2: Incidence of breast cancer according to ethnic groups in Malaysia in 2007

	No.	Crude rate	ASR	Cum. Risk
Malay	1432	21.0	25.4	2.6
Chinese	1343	43.6	38.1	4.1
Indian	297	31.5	33.7	3.6

(Source: Omar *et al.*, 2011)

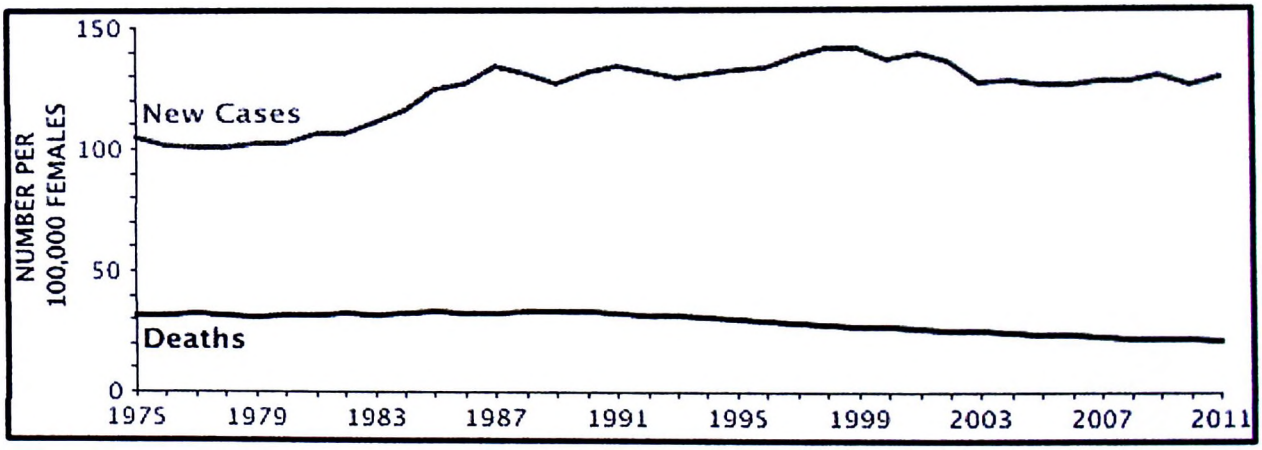

Figure 2.1: SEER 9 Incidence & U.S. Mortality 1975-2011, All races, Females. Rates are age-adjusted

(Source: Howlader *et al.*, 2015)

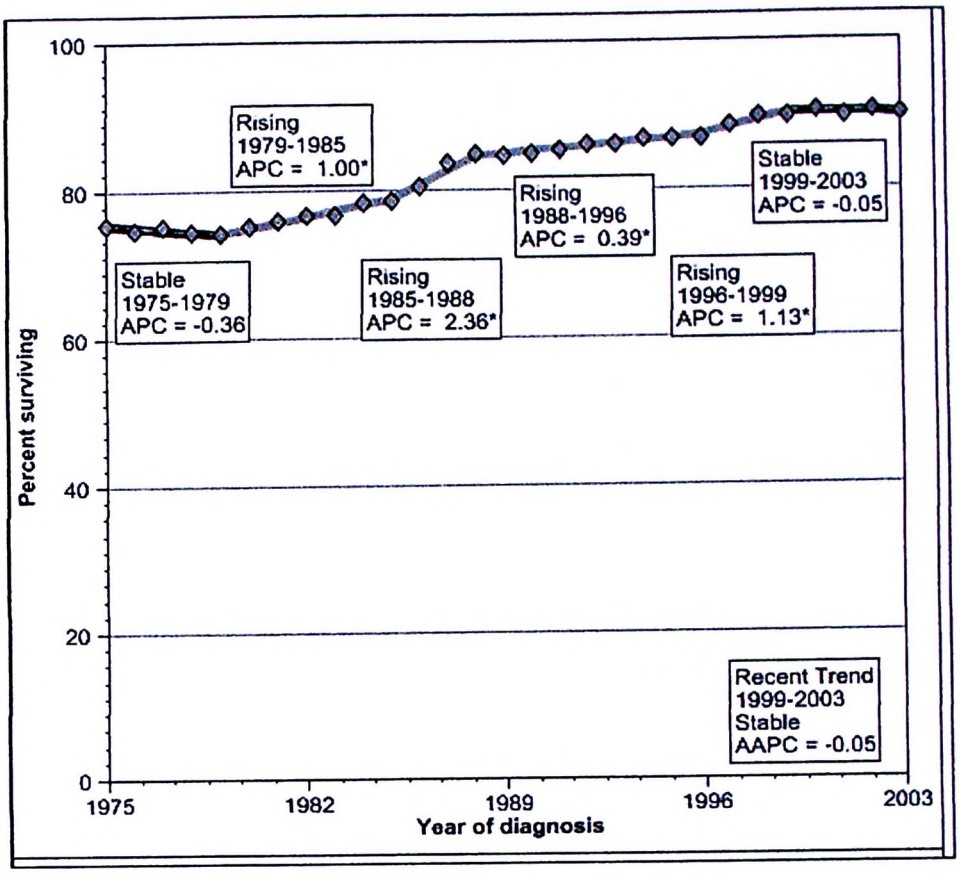

Figure 2.2: 5-year relative survival of breast cancer: 1975-2003

(Source: Howlader *et al.*, 2015)

2.3 Types of breast cancer treatment

There are six types of standard treatment used for breast cancer which is chemotherapy, radiation therapy, hormone therapy, surgery, targeted therapy, and sentinel lymph node biopsy followed by surgery. Most of these treatments produce adverse side effects.

2.3.1 Chemotherapy treatment

Chemotherapy is a cancer treatment that uses drugs to destroy cancer cells by disrupting their ability to grow and multiple. Chemotherapy can be an infusion or injection given by nurse at hospital, or it can be in pill form, which can be taken at home. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy is given depends on the type and stage of the cancer being treated (American Cancer Society, 2014).

Chemotherapy interferes with cells division cancerous cells are affected most. This is because they divide and reproduce more rapidly than normal cells. However, cells such as lining of the gastrointestinal tract are also affected as it reproduces very rapidly. This can cause side effects. The most common side effects of chemotherapy are low blood platelets, red blood cells, and white blood cells counts. Other nutrition-related side effects are inflammation of the mouth, tongue, throat, diarrhoea, constipation, milk intolerance, weakness, anaemia, weight changes, appetite changes, nausea, strange metallic taste, and vomiting (American Cancer Society, 2014).