ASSOCIATION BETWEEN NUTRITIONAL STATUS AND SERUM LEPTIN AMONG NEWLY DIAGNOSED BREAST CANCER PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HOSPITAL USM): A CASE CONTROL STUDY

by

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Thesis submitted in the fulfilment of the requirements for the degree of Master of Science

June 2016

ACKNOWLEDGMENT

In the name of Allah, the Most Gracious and the Most Merciful

Alhamdulillah, Thank You ALLAH for being beside me at every time and for giving me strength and ability to complete this thesis. I am sincerely grateful to both of my supervisors, Dr. V.M.K. Bhavharaju and Professor Dr. Wan Abdul Manan Wan Muda, for all the guidance and support throughout the duration of this study and the preparation of this thesis. May ALLAH showered with His blessings.

I would also like to thank Associate Profesor Dr. Sakinah Harith, the Dietetics Programme Chairman for her enthusiasm to encourage, motivate and support with my thesis. A special thanks to all of my colleagues in the Nutrition & Dietetics Programme, School of Health Sciences especially Associate Profesor Shariza Abdul Razak for their encouragement and also my acknowledgements are owed to the Mr Arun and Mrs Elina Husni Tan for his help in my study.

I would like to acknowledge deeply Universiti Sains Malaysia and Ministry of Science, Technology and Innovation, Malaysia (MOSTI) for funding this research and provide scholarship of my study. To the Dean, School Of Health Sciences, Profesor Ahmad Haji Zakaria, thank you for your attention, motivation and support of my study. I personally want to thanks Kak Na and Kak Ju, staffs at Post-Graduate Section, School of Medical Sciences (PPSP) for their help along my study.

Finally, I am greatly indebted to my great and beloved wife Maria Elena Razali @ Ghazali and my wonderful children Alya Nazihah, Aisyah Nazirah, Anis Nadhirah & Ahmad Nazeef for their great help, support and patient encouragement throughout my study. My deepest gratitude goes to all my family members, special thanks for motivation, support and encouragement given to me. Love you all.

May ALLAH bless.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AICR	American Institute on Cancer Research
AJCC	American Joint Committee on Cancer
BC	Breast Cancer
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BSE	Breast Self-Examination
CBE	Clinical Breast Examination
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
cm	Centimetre
CPG	Clinical Practice Guidelines
CVD	Cardiovascular Disease
DCIS	Ductal Carcinoma In Situ
DNA	Deoxyribonucleic Acid
FAO	Food and Agriculture Organization of the United Nations
FFM	Fat Free Mass
FM	Fat Mass
IKN	Institut Kanser Negara
kg	Kilogram

LABC	Locally Advanced Breast Cancer
LCIS	Lobular Carcinoma In Situ
MAKNA	Majlis Kanser Kebangsaan
MOH	Ministry Of Health
MOSTI	Ministry of Science, Technology and Innovation
NCHS	National Centre for Health Statistics
NCR	National Cancer Registry
NGOs	Non-Governmental Organizations
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of health
OR	Odds Ratio
PEM	Protein- Energy Malnutrition
RDA	Recommended Dietary Allowances
RNI	Recommended Nutrient Intake
SPSS	Statistical Package For The Social Sciences
USDA	United States Department of Agriculture
WC	Waist Circumference
WCRF	World Cancer Research Fund
WHO	World Health Organization
WHR	Waist Hip Ratio

PERKAITAN ANTARA STATUS PEMAKANAN DENGAN ARAS HORMON LEPTIN SERUM DALAM KALANGAN PESAKIT BARU KANSER PAYUDARA DI HOSPITAL UNIVERSITI SAINS MALAYSIA (HOSPITAL USM): KAJIAN KES-KAWALAN

ABSTRAK

Kadar insidens penyakit kanser payudara sedang meningkat di seluruh dunia. Di Malaysia, kanser payudara merupakan kanser yang paling ramai dihidapi oleh wanita merangkumi 29.9% daripada kes kanser yang baru. Malah, berdasarkan laporan daripada Daftar Kanser Kebangsaan (NCR), pada tahun 2006, sebanyak 3525 wanita menghidap kanser payudara di negara ini. Terdapat banyak kajian yang melaporkan bahawa berlebihan berat badan akan meningkatkan risiko mendapat kanser payudara dan individu yang gemuk mempunyai aras hormon leptin serum yang tinggi berbanding individu yang mempunyai berat badan normal. Tujuan kajian ini dijalankan adalah untuk melihat hubungan antara status pemakanan dan aras hormon leptin dalam kalangan pesakit kanser payudara baru di Hospital USM. Kajian berbentuk kes kawalan ini melibatkan seramai 46 orang pesakit kanser payudara yang baru didiagnos serta belum menerima sebarang terapi kanser dan 46 orang kumpulan kawalan berumur dalam lingkungan 20 hingga 70 tahun. Parameter yang digunakan dalam kajian untuk menilai pengambilan makronutrien ialah Ingatan Diet 1 Hari (1DDR), antropometri (berat, tinggi, indeks jisim tubuh (IJT) & ukurlilit pinggang dan pinggul) dan komposisi tubuh dengan menggunakan impedans bio-elektrikal (BIA). Aras hormon leptin serum diukur dengan kaedah '*immunoassay*' menggunakan Human Leptin ELISA Kit (AssayMax Human Leptin, Cat.No:EL2001-1;

AssayPro, USA). Setiap subjek kajian akan diambil keizinan bagi menyertai kajian ini. Secara keseluruhanya, kajian ini mendapati wanita yang mengalami haid yang awal (sebelum umur 12 tahun) dan pos menopaus masing-masing berisiko 3 kali ganda untuk mendapat kanser payudara berbanding wanita yang datang haid selepas umur 12 tahun [ORKasar=2.9 (95% CI=0.2-1.0)] ($p < 0.05$) dan pra menopaus [OR Kasar=3.0 (95% CI=1.2-7.0)] ($p < 0.05$). Indeks Jisim Tubuh (IJT) antara pesakit kanser payudara (24.5 ± 3.8 kg/m^2) dengansubjek kawalan (23.2 ± 4.8 kg/m^2) tidak berbeza secara signifikan. Peratusan lemak tubuh yang diukur dengan kaedah BIA menunjukkan perbezaan signifikan iaitu pesakit kanser payudara mempunyai aras lemak yang tinggi (36.2 ± 8.7 %) berbanding subjek kawalan (31.2 ± 8.5%)($p<0.05$) dan subjek yang mempunyai peratusan lemak tubuh (BIA) lebih daripada 32% berisiko untuk mendapat kanser payudara sebanyak 6 kali ganda [OR Kasar =5.9 (95% CI=2.4-14.4)] ($p < 0.05$) berbanding subjek yang mempunyai BIA kurang daripada 32%. 72% daripada subjek kanser payudara mengalami obesiti abdominal iaitu nisbah pinggang-pinggul (WHR) lebih daripada 0.85 berbanding 22% dalam kalangan subjek kawalan dan hasil kajian menunjukkan subjek obesiti abdominal kebarangkalian memiliki 8 kali ganda risiko untuk mendapat kanser payudara [OR Kasar= 8.0 (95% CI=3.2-20.4)]($p < 0.05$) berbanding subjek yang mempunyai nisbah pinggang-pinggul kurang daripada 0.85. Pengambilan tenaga bagi pesakit kanser payudara (1397.0±311.0 kkal/hari) secara signifikan lebih rendah berbanding subjek kawalan (1693.7±379.5 kkal/hari). Pengambilan tenaga daripada sumber protein dalam kalangan subjek kanser payudara telah melebihi Saranan Pengambilan Nutrien Malaysia (RNI) 2005. Aras hormon leptin dalam kalangan subjek kanser payudara (18.1 ± 4.63 ng/ml) secara signifikan lebih tinggi berbanding subjek

kawalan (14.7 ± 4.43 ng/ml). Hasil kajian menunjukkan wujud hubungan positif antara leptin dan BIA, ukut lilit pinggang dan nisbah pinggang-pinggul. Kesimpulanya, menarki awal (sebelum berumur 12 tahun), pos menopaus dan obesiti abdominal meningkatkan risko kanser payudara. Aras leptin yang tinggi boleh dijadikan sebagai salah satu indikator bagi risiko kanser payudara.

ASSOCIATION BETWEEN NUTRITIONAL STATUS AND SERUM LEPTIN AMONG NEWLY DIAGNOSED BREAST CANCER PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HOSPITAL USM):

A CASE CONTROL STUDY

ABSTRACT

Breast cancer incidences are increasing worldwide. In Malaysia, the most commonly diagnosed cancer among Malaysian women is breast cancer about 29.9% of new cancer cases and The National Cancer Registry (2006) reported that there were 3,525 female breast cancer cases in Malaysia. Various studies reported that excessive body weight might increase the risk of breast cancer and obese people have higher serum leptin level. This study was carried out to investigate the relationship between nutritional status and serum leptin among newly diagnosed breast cancer patients in Hospital USM. This case control study involved 46 newly diagnosed breast cancer patients who were not undergone any treatment and 46 controls aged between 20-70 years. Informed consent was obtained from each study subject. Nutritional parameters used were macronutrient intake as assessed by 1-day dietary records(1DDR), anthropometry (weight, height, waist & hip circumference, body mass index, BMI) and body composition data (bio-electrical impedance ,BIA). Serum Leptin were measured by immunoassay using Human Leptin ELISA Kit (AssayMax Human Leptin, Cat.No:EL2001-1; AssayPro, USA). Overall, early menarche were at high risk of getting breast cancer by 3 folds [Crude OR 2.9 (95% CI=0.2-1.0)] ($p < 0.05$) as compared to those who were menarche after 12 years old. Being menopause might increase breast

cancer risk by 3 folds [Crude OR 3.0 (95% CI=1.2-7.0)] ($p < 0.05$) when compared with pre-menopause study subjects. The BMI of breast cancer patients (24.5 ± 3.8 kg/m^2) and controls (23.2 ± 4.8kg/m^2) were not differed statistically ($p>0.05$). Percentage of body fat (measured by BIA) for cases (36.2 ± 8.7 %) were significantly higher compared with controls (31.2 ± 8.5%) ($p<0.05$) and subjects with BIA more than 32% were at higher risk of getting breast cancer by 6 folds [Crude OR =5.9 (95% CI=2.4-14.4)] ($p < 0.05$) compared with subjects BIA less 32%. Furthermore, 72% of breast cancer cases had abdominal obesity (WHR more than 0.85) compared to controls (22%) and the study result had shown study subjects with abdominal obesity have eight time higher risk of getting breast cancer as compared to those with waist to hip ratio less 0.85 [Crude OR= 8.0 (95% CI=3.2-20.4)]($p < 0.05$). Energy intake of cases (1397.0±311.0 kcal/d) were significantly lower than controls (1693.7±379.5 kcal/d) ($p<0.05$).The proportion of energy derived from protein in breast cancer cases was higher as the recommended nutrient intake for Malaysians (RNI) 2005. Serum leptin level was significantly higher in breast cancer cases (18.1 ± 4.63 ng/ml) as compared to controls (14.7 ± 4.43 ng/ml) ($p<0.05$). Positive relationship had been found between serum leptin level and BIA, waist and WHR, supporting the evidence that obesity was related to high leptin levels in breast cancer. In conclusion, early menarche (before 12 years old), menopause and obesity especially abdominal obesity increased breast cancer risk. Serum leptin could be an indicator for breast cancer risk.

CHAPTER 1

INTRODUCTION

1.1 Background

Breast cancer (ICD10: C50) is a cancer that forms in tissues of the breast, usually the ducts (tubes that carry milk to the nipple) and lobules (glands that secrete milk). It occurs when the cells in the ducts or lobules become abnormal and divide uncontrollably. These abnormal cells begin to invade the surrounding breast tissue and may eventually spread via blood vessels and lymphatic channels to the lymph nodes, bones, liver, brain and lungs. It is common in women compared with men. In the United State, estimated new cases and deaths from breast cancer in 2012 are 226,870 (female) and 2,190 (male). This cancer cause deaths of 39,510 among female and 410 for male (National Cancer Institute, 2012). A total of 26,089 cancers were diagnosed among all residents in Peninsular Malaysia in the year 2002 and 1 in 4 Malaysians were at great risk to get cancer. Breast cancer is the number one cause of cancer deaths in Malaysian women and it accounts for 30.4% of newly diagnosed cancer cases. The incidence continues to rise as confirmed by the second report of Malaysian National Cancer Registry (Lim, Halimah, & Lim, 2003) while the actual number of women affected by the disease could be higher than the official figures as many women fail to seek treatment for various reasons.

The aetiology of breast cancer is not fully understood but there are a number of risk factors that can lead to breast cancer. Age at menarche and menopause, diet, reproductive history, contraceptive pills, hormonal pills and genetic factors has been suggested as risk factor for breast cancer (Knoussi, 2006). One of them also is obesity as the prevalence of obesity increasing worldwide and obese women with adult weight gain seems to be at increased risk of breast cancer (IARC, 2002). Epidemiologic evidence suggested that obesity is associated with increased risk of breast cancer in women (Calle and Thun, 2004). Obese women also are susceptible to metabolic syndrome and this in turn will put them at higher risk of breast cancer. Women breast cancer patient with high BMI (overweight or obese) were 2.5 times as likely to die of their disease within 5 years of diagnosis compared with normal BMI patients (Daling, 2001).

According to World Cancer Research Fund (1997), menarche at early age, having first pregnancy at late age, late menopause and high body mass index (BMI) and overweight were associated with increased breast cancer risk. Hormone replacement theraphy, BMI and high fat and high calorie intake will increase the levels of circulating free oestrogens (Schairer *et al*., 2000 &CDC, 2012). Suga *et al*. (2001) reported that in postmenopausal women, BMI correlates with elevated expression of cyclin D1 and bcl2 mRNA in the mammary tissue, indicating that a high BMI may increase breast cancer risk by increasing serum estrogens, modulating cell cycles and inhibiting apoptosis.

Leptin is a 167 amino acid protein that is structurally related to members of cytokine family (Zhang *et al*., 1997). Leptin is mainly secreted by the white adipose tissue in direct proportion to the amount of energy stored in fat and acts by binding to specific protein receptors. Accumulating evidence suggest that the leptin is not mainly an "anti-obesity hormone" as proposed originally but is primarily a crucial endocrine factor playing an important role in the regulation of several physiological processes. As a mitogenic agent, leptin acts to promote cancer growth (Somasundar *et al*., 2003). According to Wu *et al.*, (2004), plasma leptin was significantly positively correlated with BMI, waist hip ratio and waist circumference. Excess exposure of mammary epithelium to the bioactive substances produced by adipokines at adipose tissue also can contribute to breast carcinoma – obesity and leptin is the prominent adipokine.

Nutritional and hormonal factors have been proposed to influence total leptin concentration in humans (Friedman *et al*., 1998). Macronutrients such as carbohydrate, fat and protein were found to be associated with obesity and insulin resistance. Few studies in breast cancer patients showed a direct relation between high fat intake and onset of the disease where the impact of leptin levels on the initiation and progression of breast cancer was not addressed (Kabir *et al*., 2000). The identification of prognostic factors in cancer is relevant for the clinical management of the disease. Tumour stage remains the single most important prognostic factor in many advanced cancers. However, the assessment of nutritional status could be significant in therapeutical strategy (Andreoly *et al.*, 2011). The relation of obesity as one of the risk factor for breast cancer

might be due to characterization of obese person such as an increase in adipocyte size and number, altered secretion of adipocytokine, and increased angiogenesis. This study was aimed to assess serum leptin and nutritional status among newly diagnosed breast cancer patients and the result thereafter could be useful for early detection in order to improve breast cancer outcome and survival. Prevention and early detection remains the cornerstone of breast cancer control.

1.2 Problem Statement

The most commonly diagnosed cancer among Malaysian women is breast cancer about 29.9% of new cancer cases and The National Cancer Registry (2006) reported that there were 3,525 female breast cancer cases in Malaysia. It is also the most common cancer among female and the most important cancer among population regardless of sex in Peninsular Malaysia. According to Kelantan Cancer Registry Report (2004-2008), breast cancer is the commonest among females with 439 cases with the peak age group was between 45-49 years old. The youngest age of breast cancer diagnosed in this study was 24 years old.

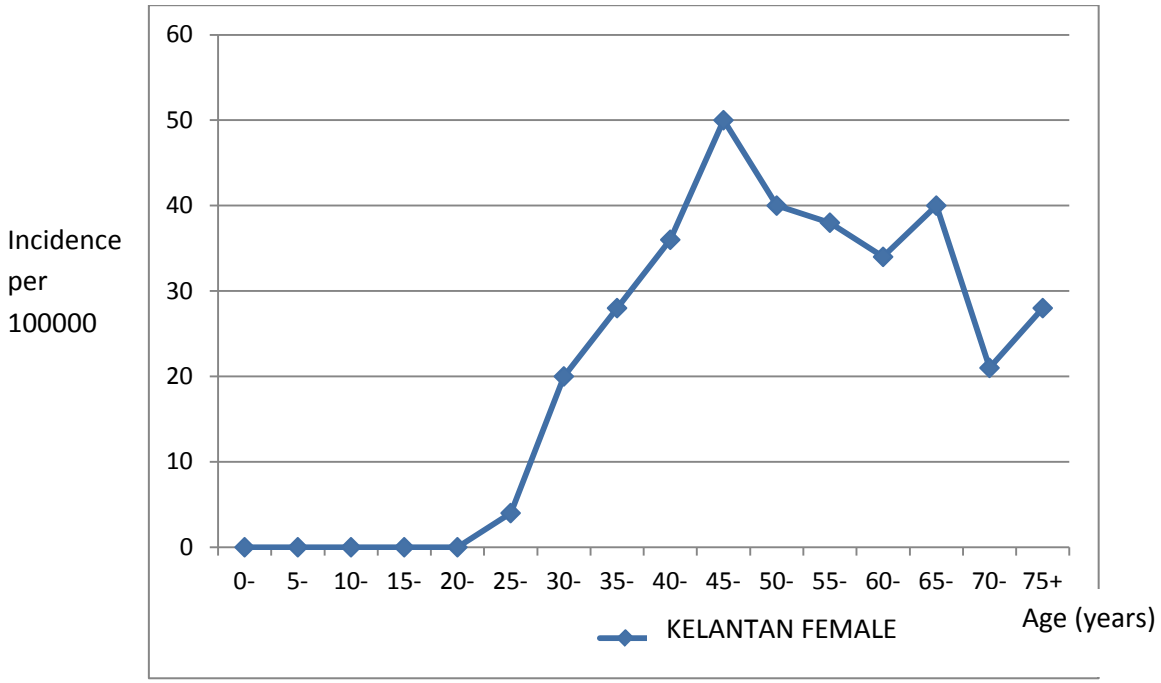

Figure 1.1: Female Breast; Age Specific Incidence Rate, Kelantan 2004 – 2009

[Adapted From: Kelantan Cancer Registry Report 2004 – 2009]

Excessive body weight and increased serum leptin level are independent risk factors for breast cancer patients in Taiwan (Chen *et al.,* 2006). Norsa'adah *et al*.(2005) had found significant risk factors of breast cancer include nulliparity, overweight or obesity, family history of breast cancer and the use of oral contraceptive among Kelantan women. But, that particular study did not look at leptin and its relation with nutritional status. Rabeta (2008), did a case control study on the relationship between lifestyles, obesity, adiponectin level and breast cancer risk, had found that adiponectin was had inverse relationship with BMI, waist circumference and body fatness. However, the study of the relationship of serum leptin, nutritional status and breast cancer are still lacking in this country. Therefore, this study was aimed to investigate the relationship of serum

leptin and nutritional status among breast cancer patients and controls. In hope that identifying modifiable risk factors can lead to earlier screening and detection of breast cancer and help in cancer prevention in this country.

1.3 Objectives

1.3.1 General Objective

To investigate the differences in concentrations of serum leptin and nutritional status in newly diagnosed breast cancer patients in Hospital Universiti Sains Malaysia (Hospital USM) and healthy women (control).

1.3.2 Specific Objectives

1. To measure and compare the nutritional status based on the data of anthropometry, body composition and macronutrient intake among newly diagnosed breast cancer patients and control.
2. To identify the association between serum leptin and anthropometry (Body Mass Index, Body Impedance Analysis, and Waist Circumference) among breast cancer patients and controls.
3. To determine the correlation between serum leptin and energy intake among breast cancer patients and controls.

1.4 Study Hypotheses

1. Ho : No difference of anthropometry, body composition and macronutrient intake among newly diagnosed breast cancer patients and control.

2. Ho : No association between serum leptin and anthropometry (BMI, BIA, Waist Circumference) among breast cancer patients.

3. Ho : No association between serum leptin and energy intake among breast cancer patients.

1.5 Conceptual Framework

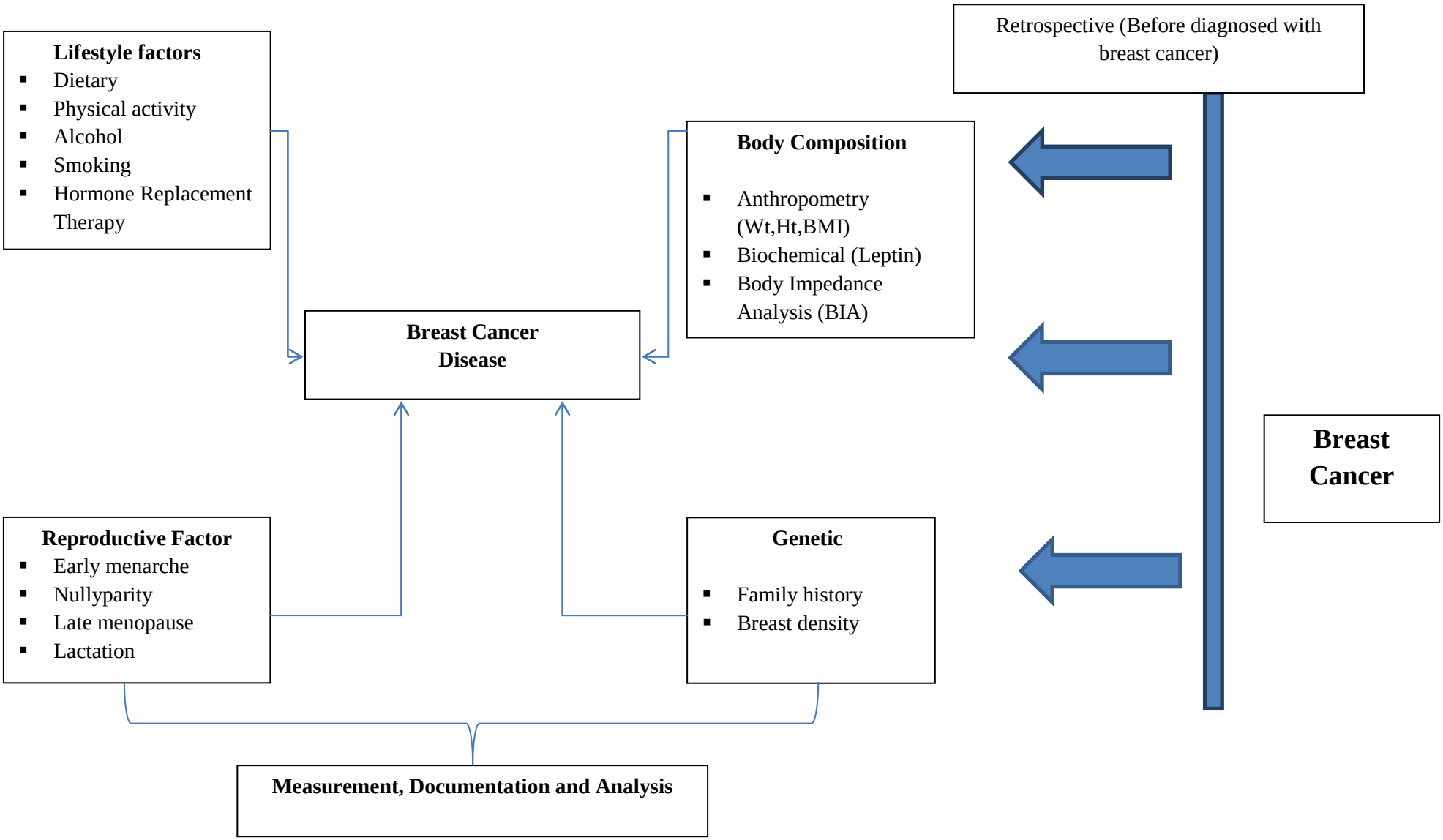

Figure 1.2: Conceptual Framework of the Study

Reference: Sahar *et al*., 2010, Rabeta M.S., 2008 & Chen *et al*., 2006

CHAPTER 2

LITERATURE REVIEW

2.1 Overview Incidence of Breast Cancer in Malaysia

The prevalence of Breast Cancer showed an increasing trend around the both developed and developing world. In 2012, about 1.7 million people had been diagnosed with breast cancer cases (World Cancer Research Fund, 2012). In Malaysia, National Cancer Registry (NCR, 2007) reported that about 3242 female breast cancer cases were diagnosed compared to 3525 new cases in 2006 (NCR, 2006). Even the number was decreased; it was still the most common cancer in females and the first most common cancer among population regardless of sex in Malaysia.

2.2 Stages of Breast Cancer

The early detection of breast cancer is very important in predicting the prognosis of a woman with this disease. Patient with late stage of breast cancer are found with larger cancer cells and are more likely to have already spread beyond the breast. In contrast, the cancer cells that are found during screening mostly are smaller size and still in-situ. There are three main activities for breast cancer screening in Malaysia which is Breast Self-

Awareness (BSA) or previously known as Breast Self-Examination (BSE), Clinical Breast Examination (CBE) and mammography screening (Maznah *et al*., 2011).

Undetected breast cancer or not treated early, can spread to breast skin and lymph nodes. Locally advanced breast cancer (LABC) includes breast cancers with large primary tumors of more than 5 cm or those with skin and/or chest wall involvement, and with or without regional lymph node involvement (Stage 3a, 3b and 3c). According to Taiplin *et al*. (2004), 52% of advanced stage of breast cancer cases were related to absence during screening programme, 39% related to absence during examination/check-up and another 8% did not undergo follow up programme. The main problem with the implementation of the programme are lack of capital and resources and low educational level had caused no mammogram breast screening program for the whole high risk women in Malaysia (Abdullah & Yip, 2004). Therefore, the numbers of breast cancer patient with late stage are increasing due to late detection. Yip *et al*. (2006) had found that almost 30-40% breast cancer patients in Malaysia were on stage 3 and 4.

Cancer stage is based on the size of the cancer, whether the cancer is invasive or non-invasive, whether lymph nodes are involved, and whether the cancer has spread to other places beyond the breast. The purpose of the staging system is to help organize the different factors and some of the personality features of the cancer into categories in order to best understand the prognosis or outcome of the disease, also to guide treatment

decisions of patient and help the patients to understand the results of the treatment (Breastcancer.org, 2013).

The most common system used to describe the stages of breast cancer is the American Joint Committee on Cancer (AJCC) TNM system (American Cancer Society, 2009). The TNM staging system classifies cancers based on their T, N, and M stages:

- The letter T followed by a number from 0 to 4 describes the tumor's size and spread to the skin or to the chest wall under the breast. Higher T numbers mean a larger tumor and/or wider spread to tissues near the breast.
- The letter N followed by a number from 0 to 3 indicates whether the cancer has spread to lymph nodes near the breast and, if so, how many lymph nodes are affected.
- The letter M followed by a 0 or 1 indicates whether the cancer has spread to distant organs -- for example, the lungs or bones.

Once the T, N, and M categories have been determined, this information is combined in a process called stage grouping.

2.2.1: Stage 0

This is ductal carcinoma in situ (DCIS), a pre-cancer of the breast & lobular carcinoma in situ (LCIS) sometimes also is classified as stage 0 breast cancer. In all cases, the cancer has not spread to lymph nodes or distant sites.

2.2.2: Stage I

i. Stage IA:

The tumor is 2 cm (about 3/4 of an inch) or less across (T1) and has not spread to lymph nodes (N0) or distant sites (M0).

ii.Stage IB:

The tumor is 2 cm or less across (or is not found) (T0 or T1) with micro metastases in 1 to 3 axillary lymph nodes (the cancer in the lymph nodes is greater than 0.2mm across and/or more than 200 cells but is not larger than 2 mm)(N1mi). The cancer has not spread to distant sites (M0).

2.2.3: Stage II

i. Stage IIA:

One of the following applies:

: The tumor is 2 cm or less across (or is not found) (T1 or T0) and either:

: It has spread to 1 to 3 axillary lymph nodes, with the cancer in the lymph nodes larger than 2 mm across (N1a), OR

: Tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1b), OR

: It has spread to 1 to 3 lymph nodes under the arm and to internal mammary lymphnodes (found on sentinel lymph node biopsy) (N1c). OR

: The tumor is larger than 2 cm but less than 5 cm across (T2) but hasn't spread to the lymph nodes (N0). The cancer hasn't spread to distant sites (M0).

ii. Stage IIB:

One of the following applies:

: The tumor is larger than 2 cm but less than 5 cm across (T2). It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1). The cancer hasn't spread to distant sites (M0). OR

: The tumor is larger than 5 cm across but does not grow into the chest wall or skin and has not spread to lymph nodes (T3, N0). The cancer hasn't spread to distant sites (M0).

2.2.4: Stage III

i. Stage IIIA:

One of the following applies:

: The tumor is not more than 5 cm across (or cannot be found) (T0 to T2). It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2). The cancer hasn't spread to distant sites (M0). OR

: The tumor is larger than 5 cm across but does not grow into the chest wall or skin (T3). It has spread to 1 to 9 axillary nodes, or to internal mammary nodes (N1 or N2). The cancer hasn't spread to distant sites (M0).

ii. Stage IIIB:

The tumor has grown into the chest wall or skin (T4), and one of the following applies:

: It has not spread to the lymph nodes (N0).

: It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1).

: It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2).

iii. Stage IIIC:

Any T, N3, M0: The tumor is any size (or can't be found), and one of the following applies:

: Cancer has spread to 10 or more axillary lymph nodes (N3).

: Cancer has spread to the lymph nodes under the clavicle (collar bone) (N3).

: Cancer has spread to the lymph nodes above the clavicle (N3).

: Cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes (N3).

: Cancer has spread to 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N3).

: The cancer hasn't spread to distant sites (M0).

2.2.5: Stage IV

Any T, any N, M1: The cancer can be of any size (any T) and may or may not have spread to nearby lymph nodes (any N). It has spread to distant organs or to lymph nodes far from the breast (M1). The most common sites of spread are the bone, liver, brain, or lung.

2.3 Breast Cancer Risk Factors

The risk factors for breast cancer in Western populations had been extensively investigated, and it has been suggested that lifestyle-related and reproductive factors were strongly associated with breast cancer (Norsa'adah *et al*., 2005). All women should understand the risk factor and update knowledge regarding breast cancer. Norsa'adah *et al*. (2005) had found that similar risk factor identified in Western populations were responsible for the occurrence of breast cancer in Kelantan. However, the information regarding risk factor of breast cancer is still low among Asian women.

There were numerous risk factors that can contribute to breast cancer and it can be divided into preventable and non-preventable. Some examples of non-preventable risk factors were genetic, breast density, reproductive history, family history, age and prior breast procedure. While, preventable risk factors were dietary habits, obesity, alcohol use and physical activity. Some of the breast cancer risks have a different role among pre menopause and post menopause women. In both premenopausal and postmenopausal women cancer risk is associated with events that alter hormonal balance, such as age at menarche, parity, body weight, body fat distribution, and use of exogenous hormones (Hong *et al*., 2004).

2.3.1 Preventable Risk Factors

Preventable risk factors are the risks that can be controlled. Many epidemiological studies have looked at the relationship between behavior and lifestyle variables on the incidence of breast cancer (Lemon *et al*., 2004).

2.3.1.1 Overweight and obesity

Dietary habit and lifestyle change have resulted in an increased number of obese people. Obesity is a condition in which a person has an abnormally high and unhealthy proportion of body fat. World Health Organization (WHO) defines obesity in terms of a scale known as the body mass index (BMI). BMI provides a more accurate measure of obesity or being overweight than weight alone (King, 2011). High BMI is generally interpreted as excess adiposity (overweight or obesity). Obesity is related to many life-threatening diseases such as cancer diabetes and cardiovascular disease. It also contributes to an acceleration of the aging process, shortening of the lifespan, depression, and a decrease in quality of life (Romao *et al*., 2008).

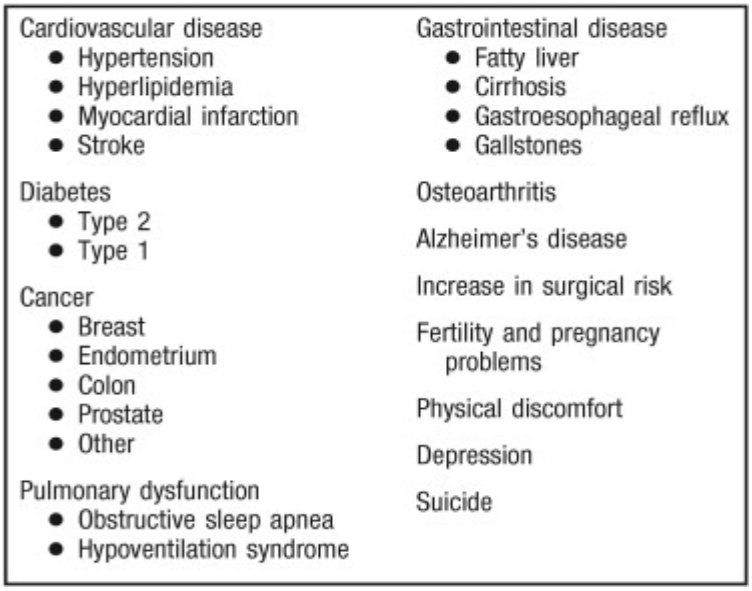

Figure 2.1. Diseases and conditions associated with obesity (body mass index ≥30; calculated as kg/m2). [Adapted from: Romao,*et al*., 2008.]

Obesity is a major health problem and is positively associated with breast cancer incidence and mortality (Barnett, 2003, Lorincz & Sukumar 2006). WCRF concluded that the associations between BMI and incidence of breast cancer were due to body fatness. The WCRF review panel concluded that weight is a factor that convincingly leads to an increase in breast cancer risk in postmenopausal women (World Cancer Research Fund, 2004) and this also has been supported by James *et al*., (2015) when they found high body mass index (BMI) is associated with increased risk of post-menopausal breast cancer and with poorer outcome in those with a history of breast cancer.

Relationship between breast cancer and obesity is not in a direct proportion (Carmichael & Bates, 2004). However, the mechanism of body weight affected breast cancer involved complex interactions between obesity, tumor biology and physiological function of the breast (Rose *et al*., 2002).

Body composition mainly consists of two components which is adipose tissue and fat free mass. This classification focused on fat because usually fat mass become main issue in health (Brodie *et al*., 1998).

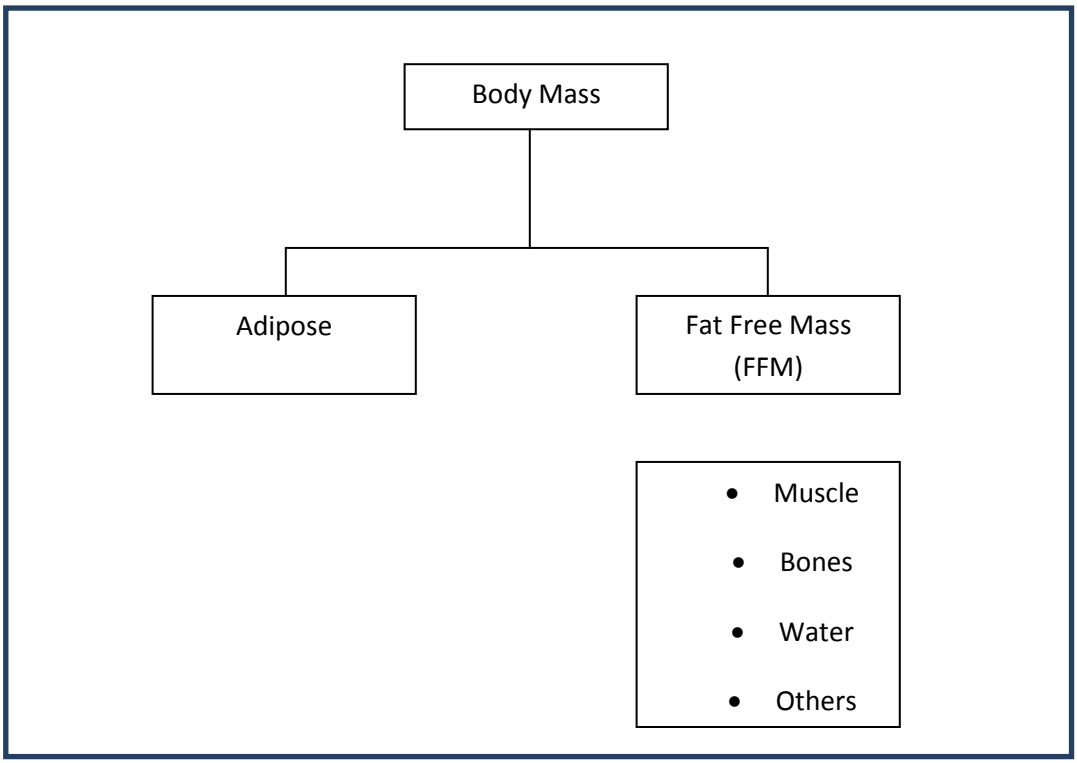

Figure 2.2: Body Composition Components

[Source: Willet, 1998]

Body composition is often defined as the ratio of fat to fat free mass and frequently is expressed as a percentage of body fat. Table 2.1 shows body fat range for persons 18 years of age and older.

Table 2.1 Body fat range for persons 18 years of age and older.

Classification	Males	Females
Unhealthy range (too low)	≤ 5%	≤ 8%
Acceptable range (lower end)	6-15%	9-23%
Acceptable range (upper end)	16-24%	24-31%
Unhealthy (too high)	≥ 25%	≥ 32%

[Source: Lee & Nieman (2007)]

i. Adipose Tissue (Fat storage)

The main role of adipose tissue is to store energy in the form of fat. However, it also provides cushions and insulates the body. Recently, research has found adipose tissue also act as endocrine organ. Adipose tissue is a source of estrogens, insulin and insulin-like growth factors, all of which are believed to be involved in mammary tumorigenesis and have been extensively evaluated as breast cancer markers and therapeutic targets (Surmacz, 2007).

Several possible mechanisms have been suggested to explain the association of obesity with increased risk of breast cancer. One of them is excess amounts of estrogen production by fat cells. The increased risk of postmenopausal breast cancer is thought to be due to increased levels of estrogen in obese women. After menopause, when the ovaries stop producing hormones, fat tissue becomes the most important source of estrogen. Because obese women have more fat tissue, their estrogen levels are higher, potentially leading to more rapid growth of estrogen-responsive breast tumors (James, 2015 & American Cancer Society, 2009).

Obese postmenopausal women have increased circulating insulin levels. Insulin stimulates the growth of breast-cancer cell lines and may increase breast cancer risk (Kaaks, 1996). Insulin-like growth factors (IGFs) are peptides that help regulate tissue growth and fat deposition (Stoll, 2000). One of these, IGF-1, stimulates mitosis in breast cancer cells. IGF-1 levels may be higher among obese women (Lipworth, 1996).

ii. Fat Free Mass

Fat free mass (FFM) is the amount of lean body. It is composed of muscle, water, bone, and other tissues devoid of fat and lipid (Lee & Nieman, 2007).

iii. Leptin

Fat cells produce hormones, called adipokines that may stimulate or inhibit cell growth (Jarde, 2011). The plasma leptin concentrations increased in direct proportion to the adipose mass (Zhang *et al.,* 2005). These two hormones were leptin and adiponectin. Leptin is a multifunctional hormone produced mainly by the adipose tissue and involved in the regulation of food intake and energy balance. It is more abundant in obese people, seems to promote cell proliferation, whereas adiponectin, which is less abundant in obese people, may have antiproliferative effects (Garotalo, 2006). Jarde (2011) had found leptin also secreted by epithelial tissue of breast tumor. Recent evidence suggests that leptin also plays an important role in normal mammary development and mammary tumor formation. Perrera (2008) suggested that leptin promotes mammary tumor growth through multiple mechanisms, including regulating the cell cycle, apoptosis, and by modulating the extracellular environment. There is increasing evidence that targeting the adiponectin:leptin ratio might be a new prognostic and/or therapeutic strategy for postmenopausal breast cancer (Jarde, 2011). Wu (2009) has shown that leptin was correlated with breast cancer risk.

2.3.1.2 Diet

There are a few dietary factors related to breast cancer risk. Among them are fiber intake and dietary fat. Unraveling links between diet and cancer is complex, as thousands of dietary components are consumed each day; a typical diet may provide more than 25000 bioactive food constituents (FAO, 2003). As shown in Figure 2.3, food can influence

fundamental processes which may promote or inhibit cancer development and progression at various ways such as metabolism of carcinogenic substances in food, apoptosis, DNA repair and hormonal regulation.

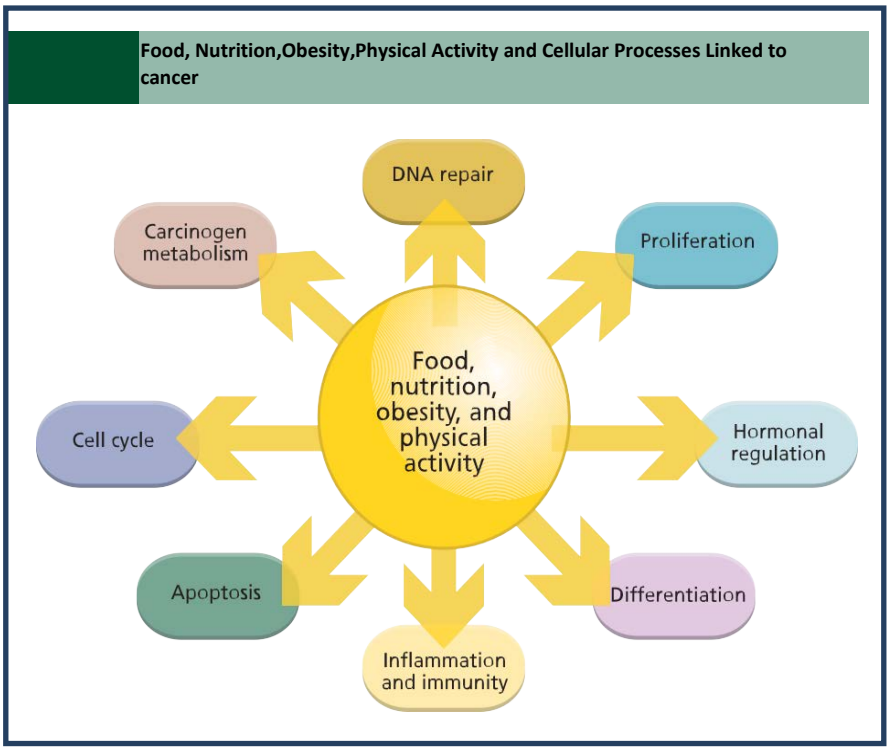

Figure 2.3: Influence of food, nutrition, obesity, and physical activity on fundamental processes shown here, which may promote or inhibit cancer development and progression
[Source: World Cancer Research Fund and American Institute for Cancer Research, 2007]

i. Excessive fat intake

Dietary fat is a macronutrient that provides energy for human body. Fat is high in calories and with small amounts can add up energy quickly. Excessive calorie intake will lead to weight gain and excessive weight is linked to risk of breast cancer. Excessive fat intake which is more than necessary for the formation of membranes and energy needs will be stored in adipose tissue and this will lead to obesity (Nik Nawal, 1998). Mattison (2004)

had showed statistically significant increased risk of breast cancer with increasing fat intake.

Dietary fat is relatively well established as a cause of increased endogenous estrogen production (Wu, 1999). Higher endogenous estrogen levels after menopause are a known cause of breast cancer (Key, 2002). Low-fat diets are usually associated with high fiber intake, which may reduce estrogen concentration by decreasing intestinal reabsorption. Another alternative mechanism by which dietary fat could influence steroid hormone levels is that increased serum-free fatty acids could displace estradiol from serum albumin, thus increasing free estradiol concentration (Burning, 1986). Sex hormone binding globulin decreases with increasing body mass index and insulin resistance. Other important factor that related with fat is energy-dense lower the age of menarche and early menarche is an established risk factor for breast cancer (American Cancer Society, 2007).

ii. Lack of fiber

Dietary fiber is all parts of plant foods that cannot be digested or absorbed by human body. Fiber can provide many health benefits such as helping to maintain a healthy weight and lower risk of diabetes, cancer and heart disease. Aune (2011) suggested that diets rich in fiber are associated with reduced breast cancer risk. Dietary fiber has been hypothesized to reduce breast cancer risk based on observations that vegetarian women