THE CORRELATION OF BODY COMPOSITION, BONE HEALTH STATUS, PHYSIOLOGICAL FUNCTION AND PHYSICAL ACTIVITY LEVEL WITH QUALITY OF LIFE AND CANCER-RELATED FATIGUE AMONG BREAST CANCER SURVIVORS IN SELECTED LOCATIONS IN MALAYSIA

AIMAN NADIA AKMAR BINTI RAHMAN

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by

AIMAN NADIA AKMAR BINTI RAHMAN

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LIST OF ABBREVIATIONS

QoL	Quality of life
CRF	Cancer-related fatigue
PA	Physical activity
SOS	Speed of sound
BMD	Bone mineral density
SF IPAQ	Short form International Physical Activity Questionnaire
BesTARI	Breast Cancer Awareness & Research (BesTARI) Unit of Hospital Universiti Sains Malaysia
BFI	Brief Fatigue inventory
BST	Back scratch test
SRT	Sit and reach test
PEFR	Peak expiratory flow rate
MPA	Moderate intensity physical activity
MVPA	Moderate-vigorous intensity physical activity
VPA	Vigorous intensity physical activity
FACT-B	Breast Cancer Functional Assessment of Cancer therapy questionnaire
PWB	Physical wellbeing
SWB	Social/family wellbeing
EWB	Emotional wellbeing
FWB	Functional wellbeing
BCS	Additional concerns for breast cancer subscale
TAHBSO	Total Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy
MET	Metabolic equivalent of task
R	Right
L	Left

LIST OF APPENDICES

KORELASI ANTARA KOMPOSISI BADAN, STATUS KESIHATAN TULANG, FUNGSI FISIOLOGI DAN TAHAP AKTIVITI FIZIKAL DENGAN KUALITI HIDUP DAN KELESUAN BERKAITAN KANSER DALAM KALANGAN PEJUANG KANSER PAYUDARA DI LOKASI TERPILIH DI MALAYSIA

ABSTRAK

Tujuan utama kajian ini adalah untuk menentukan hubungan antara komposisi badan, status kesihatan tulang, fungsi fisiologi dan tahap aktiviti fizikal dengan kelesuan berkaitan kanser dan kualiti hidup dalam kalangan pejuang kanser payudara di Malaysia. Lapan puluh tiga pejuang kanser payudara dengan purata umur 52.8 (8.7) tahun menyertai kajian ini. Para peserta menjalani penilaian komposisi badan, 'speed of sound (SOS)' tulang, dan fungsi fisiologi yang terdiri daripada kekuatan genggaman tangan, fleksibiliti bahu dan bahagian bawah badan serta fungsi paru-paru. Para peserta juga menjawab Soal Selidik Aktiviti Fizikal Antarabangsa Borang Ringkas (SF IPAQ) untuk mengenal pasti tahap aktiviti fizikal, soal selidik FACT-B untuk mengenalpasti kualiti hidup (QoL) dan soal selidik skala Inventori Kelesuan Ringkas (BFI) untuk menilai kelesuan berkaitan kanser (CRF). Hasil penyelidikan ini mendapati bahawa tiada korelasi yang signifikan antara peratusan lemak badan, dan jisim tanpa lemak dengan kelesuan berkaitan kanser dan kualiti hidup masing-masing. Korelasi negatif yang signifikan antara kekuatan genggaman tangan dan skor keseluruhan CRF (r=-0.240, p=0.032) juga diperhatikan, serta korelasi positif yang signifikan antara masa yang diluangkan untuk aktiviti fizikal sederhana hingga berat (Min/minggu MVPA) dan kesejahteraan fungsional yang merupakan komponen QoL (r=0.217, p=0.049) turut diperhatikan. Korelasi negatif yang signifikan antara bilangan hari yang diluangkan

untuk aktiviti fizikal sederhana (Hari/minggu MPA) dan keterukan kelesuan, yang merupakan satu komponen CRF (r=-0.234, p=0.033) juga diperhatikan. Korelasi negatif antara skor keseluruhan CRF dan skor keseluruhan QoL (r=-0.298, p=0.01) turut diperhatikan. SOS tulang tangan kanan didapati berkorelasi positif dengan SOS tulang tangan kiri (r=0.423, p=0.031) dan tibia kanan (r=0.264, p=0.031), fleksibiliti bahagian bawah badan (r=0.286, p=0.017) dan 'peak expiratory flow rate (PEFR)' (r=0.245, p=0.045). Analisis regresi stepwise menunjukkan bahawa pembolehubah skor kesejahteraan fizikal, skor emosi, skor fungsional, skor sosial, skor kebimbangan tambahan dan masa yang diluangkan untuk aktiviti fizikal sederhana (Min/minggu MPA) merupakan peramal signifikan untuk skor keseluruhan QoL. Peramal terbaik tunggal untuk skor keseluruhan QoL adalah skor kesejahteraan fizikal. Selain itu, didapati bahawa pembolehubah keterukan kelesuan, skor kesejahteraan fizikal, dan skor emosi adalah peramal signifikan untuk skor keseluruhan CRF. Peramal terbaik tunggal untuk skor keseluruhan CRF adalah skor keterukan kelesuan. Hasil penyelidikan ini boleh memberi maklumat baru untuk pengurusan pemulihan kanser bagi meningkatkan kualiti hidup pejuang kanser payudara.

THE CORRELATION OF BODY COMPOSITION, BONE HEALTH STATUS, PHYSIOLOGICAL FUNCTION AND PHYSICAL ACTIVITY LEVEL WITH QUALITY OF LIFE AND CANCER- RELATED FATIGUE AMONG BREAST CANCER SURVIVORS IN SELECTED LOCATIONS IN MALAYSIA

ABSTRACT

The main aim of the study was to determine relationships between body composition, bone health status, physiological functions and physical activity level with cancer-related fatigue and quality of life among breast cancer survivors in Malaysia. Eighty-three female breast cancer survivors with mean age 52.8 (8.7) years old participated in this study. The participants performed assessment of body composition, bone speed of sound (SOS), and physiological functions consisted of handgrip strength, shoulder and lower body flexibility and pulmonary function. The participants answered short form International Physical Activity Questionnaire (SF IPAQ) to identify physical activity level, FACT-B questionnaire for determining quality of life (QoL) and Brief Fatigue Inventory (BFI) scale questionnaire for assessing cancer-related fatigue (CRF). The present study found that, there was no significant correlation between percentage of body fat, and fat free mass with cancer-related fatigue and quality of life respectively. A significant negative correlation was observed between handgrip strength and total CRF score ($r=-0.240$, $p=0.032$), and a significant positive correlation was found between time spent for moderate to vigorous physical activity (Mins/week MVPA) and functional wellbeing, a component of QoL ($r=0.217$, $p=0.049$). A significant negative correlation between days spent for moderate physical activity (Days/week MPA) and severity of fatigue, a component of CRF ($r=-0.234$, $p=0.033$) was observed. A negative

correlation between total CRF score and total QoL score (r=-0.298, p=0.01) was also observed. Bone SOS of right arm was shown to be positively correlated with bone SOS of left arm (r=0.423, p=0.031) and right tibia (r=0.264, p=0.031), lower body flexibility (r=0.286, p=0.017) and peak expiratory flow rate (PEFR) (r=0.245, p=0.045). Stepwise regression analysis shows that the variables of physical well-being score, emotional score, functional score, social score, additional concern score and time spent for moderate physical activity (Mins/week MPA) reveal to be significant predictors of total QoL score. The single best predictor of total QoL score is physical well-being score. Besides, it was found that the variables of fatigue severity, physical well-being score, and emotional score are the significant predictors of total CRF score. The single best predictor of total CRF score is fatigue severity score. The present study findings could provide new information for management of cancer rehabilitation to improve quality of life of the breast cancer survivors.

CHAPTER 1

INTRODUCTION

1.1 Background of study

In Malaysia, breast cancer is ranked as the highest newly diagnosed cancer case and it is reported as the second cause of cancer death from other cancer cases. It is accounted for 34.1% of all cancer cases among females in Malaysia and only 0.5% in male (Azizah *et al*., 2019). According to Malaysia National Cancer Registry report (2019), a total of 21,634 cases of female breast cancer were diagnosed for the period of 2012-2016 compared with 18,206 cases in 5 years period before. Cancer staging (1-4) for female breast cancer in 2012-2016 was reported highest (34.5%) in stage 2 followed by 25.1% (stage 3), 22.8% (stage 4) and the least 17.5% (stage 1) (Azizah *et al*., 2019).

Survival information is an important predictor on effectiveness of cancer diagnosis and treatments, which reflects the quality of care for cancer patients. Abdullah *et al*. (2013) mentioned that the five-year survival rate for those diagnosed with breast cancer at the University of Malaya Medical Centre during last two decade was only 49%, with Indian women had higher survival rate (54%), followed by Chinese (49%) and the lowest was Malays (45%) However, the numbers are increasing by years. Based on Malaysian study for cancer survival, the relative survivor (RS) rate for breast cancer from 2007-2022 was 66.8%, in which RS rate was highest at stage 1 and Stage 2 and survival deteriorated faster at stage 3 and 4. As comparison with international countries, the Malaysian's RS rate is higher than India and Thailand, but lower than Singapore, China, Korea, Japan, Australia, New Zealand, America and other European countries. Even though there is an increasing trend of breast cancer survival rate in Malaysia, there is still a huge difference when compared to developed countries (Abdullah *et al.,* 2013).

Advancement in cancer management constitutes screening procedures and treatment interventions, and it could improve survivorship. However, cancer and its treatment undeniably causing a variety of adverse side effects. One of the side effects is changes in body composition. Bodily changes related to chemotherapy treatment includes weight gain which resulted from increase in fat mass but reduction in fat free mass, this could lead to sarcopenic obesity among breast cancer survivors (Demark-Wahnefried *et al.,* 2001). Changes in body composition such as fat mass and fat free mass impacting metabolic profiles of women with breast cancer from time of diagnosis and throughout their life, leading to development of metabolic syndrome. The clinical features of metabolic syndrome characterised by excess accumulation of adipose tissue and obesity, hypertension, dyslipidemia, insulin resistance, and increase in blood glucose (Christensen *et al.,* 2023). This condition not only affects morbidity of the cancer survivors, but also affects their involvement in physical activity, lifestyle and social life, hence may impact their quality of life (QoL).

Bone health is one of the important aspects that needs to be considered in breast cancer survivors. Breast cancer and its treatments has been reported can significantly impact bone health (Adler, 2007., Bruyère *et al.,* 2017 and Catalano *et al.,* 2019). According to Pandey *et al.* (2023) therapeutic modalities of cancer treatments such as chemotherapy, aromatase inhibitor (AI) therapy, anti-hormonal therapy can lead to deleterious effect to bone mineral density (BMD),induced secondary osteoporosis and increased risk of fractures. Consequently, this consequences toward bone health increases the risk for developing comorbid chronic disease and cancer recurrence among breast cancer survivors (Thomas *et al.,* 2017).

Cancer-related fatigue (CRF) is one of the major distresses among cancer survivors. It has been reported that breast cancer survivors with either decrease physical activity or remaining inactive had a higher risk of severe fatigue compared to those with increasing or maintaining physical activity. According to Priscilla *et al*. (2011), the prevalence of cancer-related fatigue in Malaysia is 79%, which indicates that it is very important for the public, researchers and health practitioners to prioritise this problem.

The CRF is one of the most notable symptoms associated with cancer and its treatments. Cancer-related fatigue is multifactorial and can be influenced by various demographic, medical, psychosocial, behavioural and biological factors (Bower, 2014). Exercise, physical activity and multimodal combined therapy were reported had a positive impact on severity of fatigue as well as other fitness parameters including cardiovascular endurance, muscular strength and endurance (Cantarero-Villanueva *et al.,* 2013), flexibility and improved self-regulation of breast cancer survivors (Kröz *et al.,* 2015). Studies on the prevalence and the risk factors of cancer-related fatigue had been conducted, however the findings were reported differently.

Secondary to cancer illness, cancer survivors face with changes in physiological functions which negatively affect their quality of life (QoL). It was reported that some physiological side effects faced by them including muscular atrophy, weight changes, lowered aerobic capacity, decreased strength, flexibility and fatigue (Olson *et al.,* 2017). Muscle weakness is the most common type of impairment faced by cancer survivors that contributes to functional limitation (Buffart *et al.,* 2017). Sturgeon *et al*. (2019) stated that cancer and its treatments can potentially induce lean tissue degradation and abnormalities in the metabolic system of skeletal muscle, resulting in loss of muscular strength in cancer survivors. Additionally, al-Majid & McCarthy (2001) found that patients diagnosed with cancer have increased of myofibrillar protein degradation that

is induced by tumor factors and cytokines involved in cancer, which could be associated with a loss of muscular strength in cancer survivors.

Breast cancer survivors also suffer from impaired shoulder mobility and upper limb function such as shoulder pain and reduced range of motion. Breast cancer surgery and radiation are reported contribute to these problems. Lee *et al.* (2008) stated that surgery such as axillary lymph node dissection had poorer prognosis in arm function and pain compared to sentinel lymph node biopsy. Surgical scarring, radiation fibrosis, pain, muscle weakness and compensatory posture contributes to reduce flexibility and arm function of breast cancer patients (Lovelace *et al.,* 2019)

Quality of life is a core concern for breast cancer survivors. Breast cancer survivors have gone through challenging experiences which affect their physical, emotional and social well-being. Factors associated with QoL in breast cancer patients are physical effects, in which surgeries disrupt their body image, leading to low self esteem, anxiety and depression, social effects, as well as coping and adjustment. However, due to heterogenity of sociodemographic, values and lifestyle, difference clinical characteristics, study findings in quality of life have been reported differently among breast cancer survivors. Therefore, it is important for more studies to be carried out to explore more on this topic.

Thus, this study was proposed to investigate the relationships of body composition, bone health status, physiological functions and components of physical activity level, and their relationships with cancer-related fatigue and quality of life in breast cancer survivors in Malaysia. To date, information is lacking on the influence of bone health status, physiological functions and physical activity level on cancer-related fatigue and quality of life among breast cancer survivors in Malaysia.

1.2 Problem Statement

Breast cancer survivors are at high risk of developing comorbid conditions such as osteoporosis, sarcopenia and cardiovascular disease which leads to decline in bone health, muscular strength, cardiorespiratory fitness and quality of life (Garcia & Thomson, 2014). Besides, breast cancer treatments and cancer pathology also can cause the patients to develop fatigue (Mortimer *et al.,* 2017). These negative health concerns are partly induced by cancer treatments such as chemotherapy, radiation and endocrine therapy which can be exacerbated by physically inactive lifestyle (Hege, A & Sverre,B ,2007). Besides medication, engaging in physical activity was also reported to be associated with increase in bone health and reduction in fatigue.

To date, numerous animal and human studies have been carried out to investigate the effects of physical activity ,nutritional supplementation on bone health status, bone metabolism and related physiological parameters (Ooi et al, 2009; Ooi et al, 2012; Ooi et al, 2014a; Ooi et al, 2014b; Ooi and Aziz, 2017; Sahrir et al., 2018; Mohd Zuhri et al., 2020; Ahmad et al., 2021), and these previous studies found that physical activity can elicit beneficial effects on the aforementioned parameters. Despite the wealth of research available in the field, there is a lack of clarity due to limited studies on the association of habitual physical activity with bone health and fatigue. To date, information on bone health, physical activity and cancer-related fatigue in breast cancer survivors is lacking in literature and requires further exploration. This gap in the literature highlights the need for more comprehensive studies to explore these areas, which are crucial for developing effective interventions and improving breast cancer survivors' quality of life.

Previous study that have been conducted yielded inconclusive result due to several factors such as homegeneity of the participants and strict inclusion criteria

(Muthanna *et al*., 2022). Besides, the scarcity of research about the incidence and determinants of CRF among breast cancer in Malaysia also was the main reason this study needs to be conducted. Additionally, the fact that low relative survivor rate in developing country such as Malaysia compared to other countries makes this study even more crucial (Abdullah *et al*., 2013).

Hence, the results of this study are expected to provide objective data that can help healthcare providers enhance the survivorship of cancer patients by assessing and determine factors that affecting cancer-related fatigue and quality of life of breast cancer survivors. This information is valuable for conducting thorough routine assessments of patient needs, particularly in the physical domain within oncology settings. Additionally, these findings also could guide the development of targeted interventions to support breast cancer survivors in Malaysia. Furthermore, the study may offer new clinical insights into the impact of overall physical fitness on cancer-related fatigue and quality of life which will be able to aid healthcare professionals in creating strategies to alleviate cancer-related fatigue and improve overall quality of life among breast cancer survivors in Malaysia.

1.3 Significance of the study

To the best of our knowledge, the present study is the first study which aims to explore the relationships of body composition, bone health status, physiological functions and components of physical activity level, and their relationships with cancer-related fatigue and quality of life among Malaysian breast cancer survivors in one single study. It is hoped that the findings of this study can provide new clinical evidence on the factors affecting cancer-related fatigue and quality of life among breast cancer survivors for health care professional to enhance the management on cancer

rehabilitation, and thus improving breast cancer patient's health and wellbeing. The findings of the present study will aid the cancer survivors in managing the problem of cancer-related fatigue, which indirectly may improve their cancer prognosis and survivorship. Besides, the findings of this study may provide evidence-based theory and may improve the practical aspects of cancer rehabilitation to health care providers as well as the carers particularly in Malaysia.

1.4 Research questions

1. What are the prevalence of quality of life (QoL) and cancer-related fatigue (CRF) among breast cancer survivors in Malaysia?

2. Are there any differences between age, body composition, bone health status, physiological functions, physical activity level components, quality of life (QoL) and cancer-related fatigue (CRF) based on cancer stages among breast cancer survivors in Malaysia?

3. What are the relationships of sociodemographic variables, body composition, bone health status, physiological functions, physical activity level components with quality of life (QoL) and cancer-related fatigue (CRF) respectively among breast cancer survivors in Malaysia?

4. What are the relationships among body composition variables, bone health status, physiological functions and components of physical activity level among breast cancer survivors in Malaysia?

5. What are the significant predictors and single best predictor among measured parameters in influencing total quality of life (QoL) and cancer- related fatigue (CRF) scores in breast cancer survivors?

1.5 Hypothesis of the study

H_{A1}: There are significant differences in age, body composition, bone health status, physiological functions, components of physical activity level, quality of life (QoL) and cancer-related fatigue (CRF) between categories based on stages of cancer among breast cancer survivors in Malaysia

H_{A2}: There are significant correlations of sociodemographic variables, body composition, bone health status, physiological functions, components of physical activity level with quality of life (QoL) and cancer-related fatigue (CRF) among breast cancer survivors in Malaysia.

H_{A3}: There are significant correlations among sociodemographic variables, body composition, bone health status, physiological functions, components of physical activity level, quality of life (QoL) and cancer-related fatigue (CRF) in breast cancer survivors in Malaysia.

H_{A4}: There are significant predictors of total quality of life (QoL) and cancer-related fatigue (CRF) scores among breast cancer survivors in Malaysia.

1.6 Research Objectives

1.6.1 General Objective

To investigate the relationships of body composition, bone health status, physiological functions, components of physical activity level with quality of life (QoL) and cancer-related fatigue (CRF), as well as determining the significant factors affecting quality of life (QoL) and cancer-related fatigue (CRF) in breast cancer survivors in Malaysia.

1.6.2 The Specific Objectives

The specific objectives of the study are:

1. To explore the prevalence and severity of cancer-related fatigue (CRF) and quality of life (QoL) among breast cancer survivors in Malaysia.
2. To determine the differences in age, body composition (percentage of body fat, fat free mass), bone health status (bone speed of sound) and physiological functions (handgrip strength, shoulder and lower body flexibility, pulmonary functions) between cancer stages among breast cancer survivors in Malaysia.
3. To compare the components of quality of life (QoL) and cancer-related fatigue (CRF) between categories of cancer stages among breast cancer survivors in Malaysia.
4. To determine correlations of sociodemographic variables (age, stages of cancer, period since diagnosed etc.), body compositions (percentage of body fat, fat free mass), bone health status (bone speed of sound), physiological functions (handgrip strength, shoulder and lower body flexibility, pulmonary functions) and components of physical activity level with quality of life (QoL) and cancer-related fatigue (CRF) respectively among breast cancer survivors in Malaysia.
5. To determine correlations among body compositions (percentage of body fat, fat free mass), bone health status (bone speed of sound) and physiological

functions (handgrip strength, shoulder and lower body flexibility, pulmonary function) and components of physical activity level in breast cancer survivors in Malaysia.

6. To identify the significant predictors among measured parameters in influencing total quality of life and cancer- related fatigue scores in breast cancer survivors in Malaysia.
7. To develop regression equation which imply the predictive power of variables measured in the present study.

1.7 Operational Definition

Body composition: Body composition is the proportion of fat, muscle, and bone (Messiah, 2020). In the present study, body composition parameters were determined by measurements of percentage of body fat and fat free mass.

Bone health status: The information of bone speed of sound (SOS) and T score were the parameters used to reflect bone health status of the participants in this study. Bone health status can be classified into a few categories, i.e. normal: T-score ≥ –1 standard deviation (SD); osteopenia: T-score between –1 and –2.5 SD; and osteoporosis: T-score ≤ –2.5 SD (LeBoff *et al*., 2022).

Physiological functions: Physiological function also called as body function (Roux, 2014). Participants' physiological functions were assessed via hand grip strength test, shoulder and lower body flexibility tests and pulmonary function test in this study.

Physical activity level: Physical activity defined as any bodily movement produced by skeletal muscles that requires energy expenditure (Bull *et al*., 2020). The short form International Physical Activity Questionnaire (SF IPAQ) was used to measure the physical activity level of the participants. Physical activity level can be classified into three categories, which are low, moderate and high.

Cancer-related fatigue: Cancer-related fatigue is a distressing permanent feeling of tiredness or exhaustion concerned to cancer that is not related to recent activity and interferes with common functioning (Bower, 2014). It was measured by Brief fatigue Inventory (BFI) scale questionnaire in the present study.

Quality of life: Quality of life refers to a person's perception and satisfaction with life and their general appraisal of their level of functional well-being (Pequeno *et al*., 2020). A person's perception and satisfaction with life and their general appraisal of their level of functional well-being. It was measured by FACT-B questionnaire in the current

study. The components of quality of life includes: i. physical well-being, ii. social/family well-being, iii. emotional well-being, iv. functional well-being, and iv. additional concerns for breast cancer.

Breast cancer survivors: Any person who has been diagnosed with breast cancer starting from the time of diagnosis through the remaining years of life. In the present study, breast cancer survivors between 25 and 75 years of age from stage 1 to stage 4 were recruited.

1.8 Conceptual Framework

Based on the information obtained from literature review, it is hypothesised that there are close relationships between body composition, bone health status, physiological functions, physical activity level with cancer-related fatigue and quality of life in breast cancer survivors. Therefore, the conceptual framework of the present study was proposed (Please refer to Figure 1.1). The conceptual framework shown in Figure 1.1 illustrates how low physical activity, poor body composition, reduced physiological functions, and poor bone health status interact to increase the severity of cancer-related fatigue. Low physical activity contributes to reduced muscular strength, flexibility, and pulmonary function, leading to poor body composition and bone health status as indicated by decreased value of bone speed of sound (SOS). These interconnected factors create a cycle where diminished physical condition and health status worsen cancer-related fatigue. All these factors will affect the overall quality of life. The hypothesised framework highlights the importance of addressing all these areas in managing cancer-related fatigue among breast cancer survivors to improve overall quality of life of breast cancer survivors.

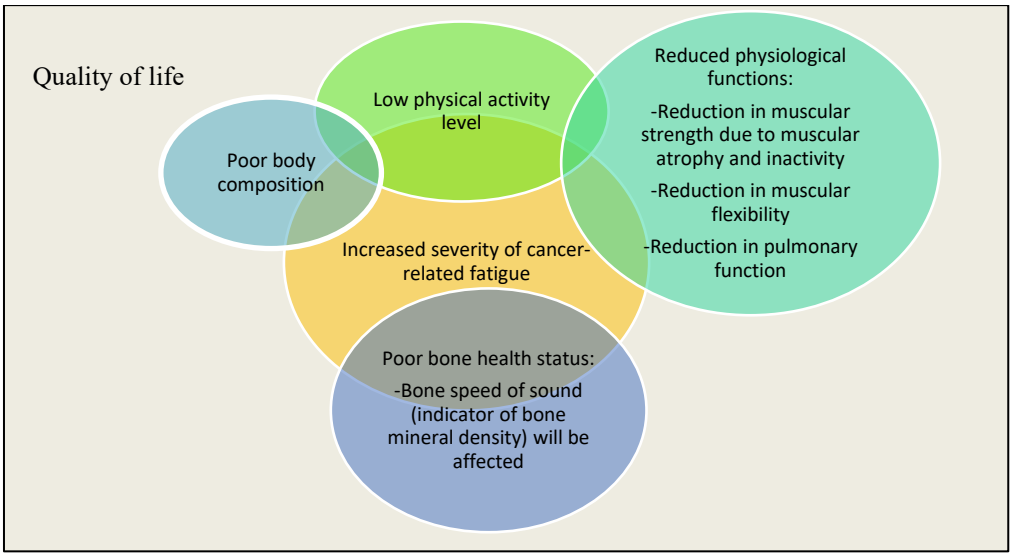

Figure 1.1 Speculated relationships between body composition, bone health status, physiological functions, physical activity level with cancer-related fatigue and quality of life in breast cancer survivors.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction to breast cancer

Cancer is one of the leading causes of morbidity and mortality worldwide. It is the second leading cause of death globally and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer. A research reported that 70% of cancer deaths occur in low- and middle-income countries (Bray *et al.,* 2018). In Malaysia, breast cancer is ranked as the top or highest newly diagnosed cancer case (17.3%) and reported as the second cause of cancer death (11.0%) out of other cancer cases. Breast cancer is also the most common form of malignancy that affecting female population in Malaysia (Bray *et al.,* 2018). Breast cancer is defined as the tumor of the breast. There are many terms used for describing breast cancer such as breast neoplasm, breast carcinoma, mammary neoplasm, mammary cancer, breast malignant neoplasm, breast tumor, breast neoplasm and more (*Breast Neoplasms - MeSH - NCBI*, n.d.).

Breast cancer is a complex disease at the morphological, molecular and genomic level, defining subtypes with distinct biological and clinical features. Studies profiling gene expression classified breast cancers into five distinct subtypes: 1.luminal A (ER positive and/or PR positive, human epidermal growth factor receptor 2 (HER-2) negative), 2. luminal B (ER positive and/or PR positive, HER-2 positive), 3.HER-2 overexpressing (ER negative, PR negative, HER-2 positive), 4. basal-like (ER negative, PR negative, HER-2 negative, cytokeratin 5/6 positive and/or epidermal growth factor receptor positive) and 5. normal breast-like tumors (unclassified) (Carey *et al.,* 2006). Expression of hormone receptors (HR), estrogen receptor (ER) or progesterone receptor (PR) distinguishes two classes of tumors and derive from different cells of origin: HR+

tumors deriving from luminal epithelial cells and HR− from basal/myoepithelial cells (Abubakar *et al.,* 2018). Whereas the human epidermal growth factor receptor 2 (HER2) are cancers that tend to be aggressive and fast-growing. Its overexpression occurs in 10-20% of breast cancers and said to be poorer prognosis.While invasive breast cancer can be categorised into two types, which are invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). ILC is hormonally mediated, more common in older age, tends to be multicentric, estrogen/progesterone receptor (ER/PR) positive and HER2-neu negative (Iqbal & Iqbal, 2014).

2.2 Stages and severity of breast cancer

According to Amin *et al.* (2017), the staging of breast cancer is used to describe how far the cancer has developed and spread at time of diagnosis. The cancer stages can be described by TNM system. Diagnostic tests are administered to rule out the stages of breast cancer by identifying the tumor (T) clinical and pathological characteristics. The tumor size was measured and its biomarkers were identified. The regional criteria of the lymph nodes (N) also were assessed clinically and pathologically. Lastly, the metastasis (M) category ware assessed based on clinical, radiographic and histological investigations. In Malaysia, currently the clinical guideline of breast cancer staging was made based on The American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th Edition).

Breast cancer and other cancer also can be categorised based on numbered system. The numbered system of cancer stage classification started with stage 0, stage 1, stage 2, stage 3 and stage 4. The given numbers showed how far the cancer has spread. Stage 0 cancer is described as availability of abnormal cell but have not spread from where they started. This stage also referred as “in situ”cancer. Stage 1 cancer is

characterized by small cancer and has only spread into nearby tissue. However, it did not spread to other body areas or the lump nodes. Stage 2 and stage 3 are stages when cancer has spread into nearby tissue or lymph nodes. Lastly is stage 4. This category indicates the cancer has spread to other areas of the body. Stage 4 is also called as metastatic cancer or advanced cancer (Maughan *et al.,* 2010)

2.3 Cancer-related fatigue (CRF)

One of the most frequent adverse effects reported in cancer patients undergoing systemic treatments is fatigue. Cancer-related fatigue has been identified as one of the top five first-tier high-priority research areas by the National Cancer Institute of United State of America (USA). CRF is one of the most notable symptoms associated with cancer and its treatments, with the greatest negative impact on quality of life. It is described as a distressing permanent feeling of tiredness or exhaustion concerned to cancer that is not related to recent activity and interferes with common functioning (Tabrizi & Alizadeh, 2017). Study showed that fatigue levels were high during chemotherapy and at the end of the chemotherapy session, maintaining after 1 year and only declining up to ten year (Fabi *et al.,* 2017).

Fatigue in various disease conditions is thought to be multifactorial in nature and encompasses both physical and cognitive aspects (Feng *et al.,* 2019). In cancer patients, CRF can be caused by the underlying disease, comorbid symptoms, medical conditions, as well as treatment received (Mortimer *et al.,* 2017). It is more severe in patients who receive more than one type of treatment. Fatigue is seldom an isolated symptom, but generally it is with components of symptom complex that may include depression, anxiety, and sleep disorders. Consequently, CRF leading survivors to depend on others for home management, transportation and even self-care activities

which is demoralizing and discouraging. Furthermore, CRF forces patients to engage in unwanted activities in an attempt to cope with their fatigue, such as lying down or taking naps which indirectly lead to physical decondition. A study stated that CRF is considered more distressing and has a great negative impact on patients' daily activities and quality of life (Mustian *et al.,* 2012).

2.4 Cancer-related fatigue among breast cancer survivors

Fatigue is one of the major problems faced by breast cancer survivors. According to Matias *et al.* (2019), 51.5% of patients experienced severe fatigue 2 years post-diagnosis. In addition, 53.3% of patients either decreased physical activity or remained inactive at 2 years postdiagnosis. At 2 years post diagnosis, it is reported that patients with decreasing physical activity or remaining inactive from pre- to postdiagnosis had a higher risk of severe fatigue compared to those with increasing or maintaining physical activity. Puigpinós-Riera *et al.* (2020) mentioned that seventy two percent, 72% of breast cancer survivors in DAMA cohort study reported having moderate to severe fatigue. Additionally, severe fatigue was greatest among individuals with low social class, those aged under 50 years, those with chronic disorder who had relapsed and those with symptoms of anxiety and depression The authors also mentioned that CRF was not related to the stage of cancer diagnosis or time since diagnosed. Aleixo *et al.* (2020) reported that breast cancer patients with lower skeletal muscle index (SMI) indicated as sarcopenia and have lower BMI had lower fatigue scores .

Involvement in physical activity for cancer survivors should be encouraged to cope with the severity of fatigue. Besides, exercise and physical activity is a nonpharmacological, low-cost approach, with the potential to improve or maintain bone

health and additional likely benefits to cardiovascular fitness, body weight management, balance, and risk for falling. In the present study, physical activity level of cancer survivors was assessed, and the relationship of physical activity level with cancer-related fatigue was determined.

2.5 Mechanism of cancer-related fatigue

Cancer-related fatigue (CRF) causes reduction in all aspects of quality of life and might be a risk factor of reduced survival. There is growing understanding of the underlying biological mechanisms. Several mechanisms had been proposed on the causes of CRF such as proinflammatory cytokines (Schubert *et al.,* 2007) hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Schubert *et al.,* 2007), circadian rhythm desynchronization (Berger *et al.,* 2010), skeletal muscle wasting (al-Majid & McCarthy, 2001) and genetic dysregulation. However, there is a considerable variability in the presentation of cancer-related fatigue, much of which is not explained by disease-related or treatment-related characteristics.

According to Saligan *et al.* (2015), previous research studies associations between inflammatory biomarkers and CRF. For instances, several studies studied the associations between concentrations of cytokines such as interleukin (IL)-6 or its receptors, TNF-α have most often been investigated in association with CRF, but results are inconsistent. Besides, results were also reported for Interleukin 1 receptor antagonist (IL1-ra), soluble tumor necrosis factor receptor type 2 (sTNF-R2), as well as C-reactive protein (CRP).

In biological nature, inflammatory process is involved in the aetiology of cancer related fatigue (Figure 2.1). According to Bower (2014), proinflammatory cytokines, including interleukin (IL) IL-1β, Tumor Necrosis Factor (TNF) TNF-α, and IL-6, are

released by immune cells following infection or tissue injury. In the context of cancer, proinflammatory cytokines may also be released by the tumour itself, tissue damage from surgery, radiation, or chemotherapy. These cytokines can signal to the central nervous system, leading to symptoms of fatigue and other behavioural changes.

Fatigue and inflammatory processes may also be influenced by psychological and behavioural processes and neuroendocrine dysregulation. Alterations in the cellular immune system, which can arise following cancer treatment, might also contribute to persistent inflammation and associated symptoms of fatigue. Furthermore, the presence of single nucleotide polymorphisms (SNPs) in genes that regulate proinflammatory cytokine expression also found to be linked to cancer-related fatigue (Bower, 2014).

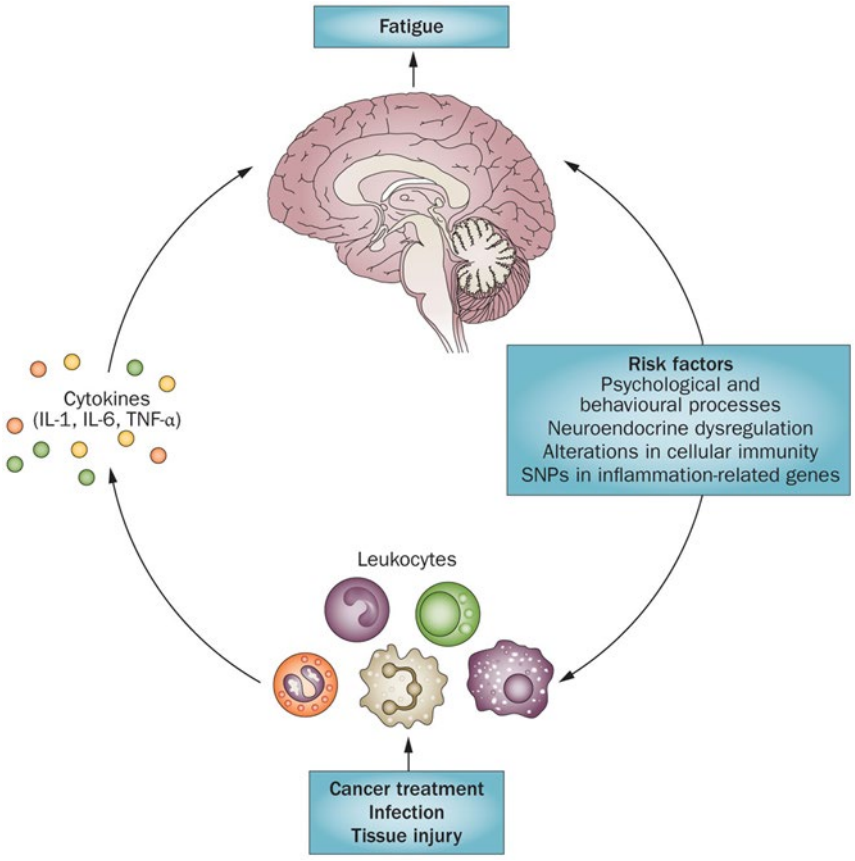

Figure 2.1 Mechanism of cancer-related fatigue

2.6 Physical activity and breast cancer survivors

A review conducted by Kim *et al.* (2013a) reported that engaging in physical activity among breast cancer survivors was significantly associated with decreased mortality, increased physiological functions, and changes in metabolic biomarkers. The major health outcomes were the increased cardiorespiratory functions, muscular strength, and immune cell components. Particularly, aerobic training was significantly associated with increasing cardiorespiratory functions such as improvement in maximum and peak oxygen uptake and decreased blood pressure, while resistance training was significantly associated with increasing muscular strength such as the increase of upper-lower body strength, hand grip strength and flexibility.

Mishra *et al.* (2012), reported that exercise and physical activity are able to affect the physiological changes, improving the quality of life of breast cancer survivors in terms of body image or self-esteem, sexuality, sleep disturbance and social functioning. Furthermore, exercise interventions may also result in decreased anxiety, fatigue and pain. Thus, examination of factors which influence engagement in physical activity and exercise in breast cancer survivors is a prerequisite to interventions aims at increasing their behaviors toward exercise.

It has been mentioned in Hirschey *et al.* (2018) that according to American Cancer Society, the recommended exercise and physical activity for breast cancer survivors are strength training for 2 times per week and exercise weekly with minimum of 75 minutes of vigorous intensity, or performing moderate intensity exercise for 150 minutes per week. It was also mentioned that those who follow the recommended exercise gained benefit of 40% lower mortality risk and decreased fatigue level. Unfortunately, in USA, only 33% of breast cancer survivors meet the exercise recommendations. According to Yaw *et al.* (2014), in Malaysia, only 22.6% of the

women increased their physical activity since diagnosis of cancer. Intensity of physical activity may play a significant role in study designs, nevertheless the level of intensity was not consistently reported. Many previous studies recommended moderate intensity physical activity, while several studies recommended vigorous intensity physical activity. However, these studies do not provide conclusive evidence about which physical activity intensity is more beneficial to survivors (Kim *et al.,* 2013a).

According to de Boer *et al.* (2017), although many studies show an association between physical activity and breast cancer risk, the precise quantitative characteristics, like type, dose and timing of the activity may have a different influence on the breast cancer risk. There are four types of physical activity: occupational activity, household activity, recreational (also called leisure) activity and transportation (from and to work) activity. Even though different types of activity were all associated with a significant reduction of breast cancer risk, the recreational activity showed profound effect compared to others.To date, the most appropriate prescription of the physical activity is still inconclusive in literature review.

2.7 Physiological functions and cancer survivors

According to Lovelace *et al.* (2019), breast cancer survivors may experience physiological and physical changes such as anatomic changes, chronic pain, lymphedema, decreased strength, changes in aerobic capacity, mobility, fatigue and cognitive dysfunction. In addition, Olson *et al.* (2017) also reported some physiological side effects faced by breast cancer survivors including muscular atrophy, weight changes, lowered aerobic capacity, decreased strength, decreased flexibility and fatigue. Changes in physiological functions could negatively affect quality of life in cancer survivors.

With the advancement of cancer treatment, breast cancer survivors who had undergone primary cancer treatments are expected to return to their daily life and work at a level like before the cancer diagnosis. However, it is important to aware that the cancer treatments received by cancer patients also leading to prolonged side effects and complications that hindering them from return to their normal daily life. It has been reported that cancer and its treatments leading to physical and psychosocial health problems such as pain, cancer-related fatigue (CRF), psychosocial and psychological distress (Aaronson *et al.,* 2014). These problems lead to profound impact on physical and psychosocial functioning.

Adverse health outcomes always can be seen in breast cancer survivors due to prolonged treatment with side effects, such as loss of energy and lack of physical strength (Kim *et al.,* 2013b). Muscle weakness is the most common type of impairment faced by cancer survivors that contributes to functional limitation (Buffart *et al.,* 2017). Besides, cancer and its treatments can potentially induce lean tissue degradation and abnormalities in the metabolic system of skeletal muscle, resulting in loss of muscular strength in cancer survivors (Sturgeon *et al.,* 2019). A study by al-Majid & McCarthy, (2001), found that patients diagnosed with cancer have increased of myofibrillar protein degradation that is induced by tumor factors and cytokines involved in cancer, which could be associated with a loss of muscular strength in cancer survivors.

Upper limb dysfunction such as decrease shoulder range of motion (ROM), pain and lymphedema are commonly reported side effect of breast cancer treatment. Structured exercise and physical therapy conducted early weeks following surgery reported produce significant result to overcome the upper limb dysfunction (McNeely *et al.,* 2010). According to Yang & Kwon (2018), shoulder muscle activity is significantly affected by breast cancer surgery tru several ways for example altered