THE EFFECTS OF COMBINED OMEGA-3 AND VITAMIN D SUPPLEMENTATION ON NUTRITIONAL STATUS, QUALITY OF LIFE AND INFLAMMATORY BIOMARKERS AMONG THE BREAST CANCER WOMEN IN GAZA STRIP, PALESTINE: A RANDOMISED CONTROLLED TRIAL

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ALA	Alpha linoleic acid (α-linolenic acid)
BC	Breast cancer
BMI	Body mass index
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
BSE	Breast self-exams
CC	Calf Circumference
CT	Chemotherapy
DHA	Docosahexaenoic Acids
ELISA	Enzyme Linked Immunosorbent Assay
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EORTC QLQ-BR23	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-breast 23
EPA	Eicosatetraenoic acid
ER	Estrogen receptors
ESPEN	European Society for Clinical Nutrition and Metabolism
FAs	Fatty acids
HER2	Human epidermal growth factor receptor-2
hsCRP	Human sensitive C-reactive protein
IDC	Invasive (infiltrating) ductal carcinoma
ILC	Invasive lobular carcinoma
IL-6	Interleukin 6
IL-1β	Interleukin- 1β
IL-10	Interleukin 10
IPAQ-S	International physical activity questionnaire short form
LMIC	Low and middle income countries
25(OH)D	25-hydroxyvitamin D
PA	Physical Activity
PG-SGA	Patient-Generated Subjective Global Assessment
PR	Progesterone receptors

PUFAs	Polyunsaturated fatty acids
QoL	Quality of life
RDA	Recommended Dietary Allowance
TG	Triglyceride
TNF-α	Tumor Necrosis Factor-alpha
VitD	Vitamin D
ω3	Omega-3 fatty acids
WC	Waist circumference
WHO	World Health Organization

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KESAN GABUNGAN SUPPLEMENTASI OMEGA-3 DAN VITAMIN D TERHADAP STATUS PEMAKANAN, KUALITI HIDUP DAN PENANDABIO RADANG DALAM KALANGAN WANITA KANSER PAYUDARA DI SEMENANJUNG GAZA, PALESTIN : KAJIAN RAWAK TERKAWAL

ABSTRAK

Kanser payudara (KP) merupakan punca utama kematian berkaitan kanser di seluruh dunia, terutamanya dalam kalangan wanita. Penjagaan pemakanan awal adalah penting untuk mencegah cachexia kanser, meningkatkan kesihatan keseluruhan, dan kualiti hidup (QoL) bagi pesakit KP. Kajian ini bertujuan untuk menilai kesan suplemen asid lemak omega-3 (ω3) dan vitamin D_3 (VitD) terhadap status pemakanan, QoL, penandabio keradangan, dan pengambilan diet dalam kalangan wanita yang baru didiagnos KP di Semenanjung Gaza, Palestin. Dalam percubaan rawak, terkawal, berlabel terbuka selama 9 minggu ini, seramai 96 peserta telah diagihkan secara rawak ke dalam salah satu daripada empat kumpulan iaitu, i) kumpulan ω3, ii) kumpulan VitD, iii) kumpulan ω3+VitD, dan iv) kumpulan kawalan. Kumpulan intervensi menerima sama ada dua kapsul 300mg ω3 setiap hari dan/atau satu tablet 50,000 IU VitD mingguan. Faktor hasil kajian termasuk skor penilaian global subjektif (PG-SGA)-berdasarkan pesakit, pengukuran antropometrik, analisa pengambilan diet melalui 24 jam yang lepas, dan penilaian QoL menggunakan dua penilaian dari EORTC QLQ-C30 dan QLQ-BR23, serum albumin , serum *tumour necrosis factor-alpha* (TNF-α), serum *C-reactive protein* (hsCRP). Daripada keseluruhan 96 peserta, 88 telah berjaya menyelesaikan kajian, di mana pencapaian kadar tindak balas kajian adalah 91.7%. Terdapat peningkatan ketara dalam skor risiko pemakanan yang

diperolehi PG-SGA (p<0.01), berat badan, dan indeks jisim badan (IJT) (kedua-duanya dengan p<0.05) dalam kumpulan ω3+ VitD berbanding kumpulan yang lain. Tambahan pula, terdapat peningkatan yang ketara dalam tahap serum albumin (p<0.05), berbanding bacaan dasar dalam kumpulan ω3+ VitD. Analisa pengambilan nutrien pemakanan telah menunjukkan peningkatan yang ketara dalam pengambilan harian tenaga dan protein dalam kedua-dua kumpulan ω3+VitD dan kumpulan ω3 sahaja (kedua-duanya dengan p<0.05) berbanding dengan bacaan dasar. Perbezaan ketara dalam jumlah status kesihatan global (p<0.01) dalam kalangan kumpulan ω3+VitD diperolehi berbanding kumpulan yang lain, dan peserta dalam kumpulan ω3+ VitD telah melaporkan skor fungsian yang lebih tinggi dengan ketara (semuanya dengan p<0.05), dan skor yang lebih rendah bagi keletihan (p<0.01), loya dan muntah, sakit, dan kehilangan selera makan (semuanya dengan p<0.05), berbanding dengan bacaan dasar masing-masing. Selain itu, peserta di kumpulan ω3+VitD menunjukkan pengurangan ketara dalam penanda bio iaitu hsCRP dan TNF-α (kedua-duanya dengan p<0.05) daripada bacaan dasar, dan perbezaan ketara dalam TNF-α (p<0.05) dan hsCRP (p<0.001) telah ditunjukkan antara kumpulan di akhir intervensi. Secara keseluruhan, gabungan suplemen ω3 dan VitD telah meningkatkan dengan ketara status pemakanan, QoL dan penandabio keradangan dalam kalangan wanita KP yang dalam proses rawatan aktif. Penemuan ini menekankan potensi penggunaan suplemen ω3 dan VitD sebagai terapi tambahan yang berkesan dalam rawatan KP untuk meningkatkan kualiti kesihatan dan mengurangkan keradangan, terutamanya dalam keadaan sumber kesihatan yang terhad. Oleh itu, garis panduan pemakanan dan intervensi yang disesuaikan adalah penting untuk mengoptimumkan integrasi penjagaan pemakanan dalam penjagaan perubatan onkologi

THE EFFECTS OF COMBINED OMEGA-3 AND VITAMIN D SUPPLEMENTATION ON NUTRITIONAL STATUS, QUALITY OF LIFE AND INFLAMMATORY BIOMARKERS AMONG THE BREAST CANCER WOMEN IN GAZA STRIP, PALESTINE: A RANDOMISED CONTROLLED TRIAL

ABSTRACT

Breast cancer (BC) is a leading cause of cancer-related mortality worldwide, particularly among women. Early nutritional care is essential to prevent cancer cachexia, improve overall health, and enhance the quality of life (QoL) for BC patients. This study aimed to assess the impact of omega-3 fatty acids (ω3) and vitamin D3 (VitD) supplementation on nutritional status, QoL, blood biomarkers, and dietary intake in newly diagnosed BC women in Gaza, Palestine. In this 9-week randomized, controlled, open-labelled trial, 96 participants were recruited and randomly assigned to one of four groups: i) ω3 group, ii) VitD group, iii) ω3+VitD group, and iv) control group. The intervention groups received either two daily 300mg ω3 capsules and/or one weekly 50,000 IU VitD tablet. Outcome measures included patient-generated subjective global assessment (PG-SGA) scores, anthropometric measurements, dietary intake analysis via 24-hour recall, and QoL assessments using the EORTC QLQ-C30 and QLQ-BR23, serum albumin, serum tumour necrosis factor-alpha (TNF-α), serum high-sensitive C-reactive protein (hsCRP). Of the total 96 participants, 88 had completed at the end of study, achieving a 91.7% response rate. There was a significant increase in PG-SGA-derived nutritional risk scores (p<0.01), body weight, and body mass index (BMI) (both p<0.05) in the ω3+ VitD group compared to other groups. Furthermore, there was a significant rise in blood albumin levels (p< 0.05) compared

to baseline in the ω3+ VitD group. Dietary nutrient intake analysis demonstrated substantial increases in daily energy and protein intake in both the ω3+VitD group and the ω3 group alone (both $p<0.05$) compared to the baseline. Significant differences in total global health status ($p<0.01$) among ω3+VitD group were observed compared to other groups, and women in the ω3+ VitD group reported significantly higher functional scores (all $p<0.05$), and lower scores for fatigue ($p<0.01$), nausea and vomiting, pain, and appetite loss (all $p<0.05$), compared to the baseline. Notably, the ω3+ VitD group showed a significant reduction in serum hsCRP and TNF-α (both $p<0.05$) from the baseline, and significant differences in TNF-α ($p<0.05$) and hsCRP ($p< 0.001$) were noted between groups at the trial's end. Overall, combined ω3 and VitD supplementation significantly improved nutritional status, QoL, and inflammatory markers among BC women who had undergoing an active treatment. These findings highlight the potential use of ω3 and VitD supplements as an effective adjuvant therapy in BC patient management, improving health outcomes and reducing inflammation, particularly in resource-limited settings. Hence, tailored nutritional guidelines and interventions are crucial for optimizing their nutritional care integration into the medical oncology care.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

A growing body of evidence has suggested that cancer is a leading cause mortality worldwide, along with other chronic diseases such as cardiovascular diseases, diabetes and stoke (Bray *et al*., 2021). Based on the recent report of GLOBOCAN 2020 on the global cancer burden, published by the International Agency for Research on Cancer had reported that about 2.3 million new cancer bases and almost 10.0 million cancer mortality occurred in 2020 (Sung *et al*., 2021). It is estimated that one in 5 people could develop cancer during their lifetime globally and one in 8 men and one in 11 women die due to cancer. In addition, the burden of cancer globally has been expected to increase to 28.4 million cases in 2040, which is almost 50% increase from 2020 with more cases found in transitioning countries (64% to 95%) in comparisons to transitioned countries (32% to 56%) (Sung *et al*., 2021).

It is well well-established that breast cancer (BC) is the most common malignant disease among women (Bray *et al.*, 2018), accounting for about 25% of cases. It is followed by colorectal cancer, lung and bronchus cancer, and uterine cancer (Figure 1.1). Notably, BC represents 1 in 4 newly diagnosed cancers in women (Sung *et al*., 2021). In 2020, BC is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths globally (Sung *et al*., 2021). The incidence rate of BC varies significantly between regions. It was 88% higher in transitioned countries compared to transitioning countries (55.9 vs. 29.7 per 100,000, respectively). However, BC mortality rates were notably higher in transitioning countries (15.0 per 100,000) than in transitioned countries (12.8 per 100,000) (Sung *et al*., 2021). In Palestine, based on annual official report from the Ministry of Health in 2022, a total 934 new cases had

diagnosed with BC, in which 15.8% was attributed to BC in West Bank and 19.2% in Gaza Strip (MOH Palestine, 2022).

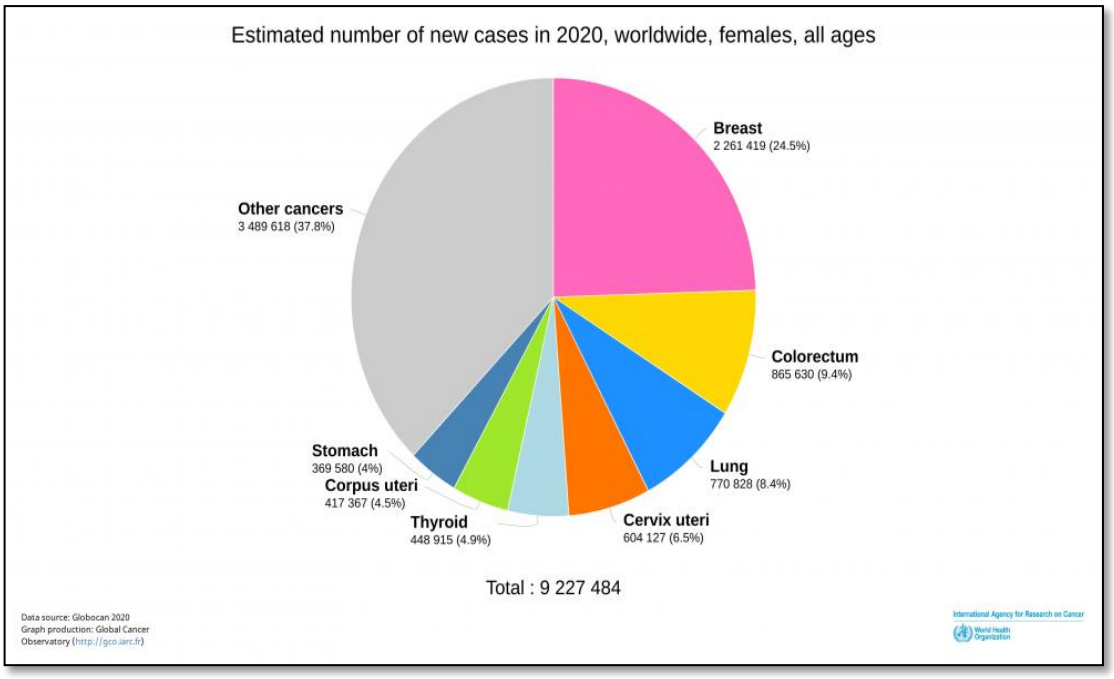


Figure 1.1 Total estimated number cases based on types of cancer in females of all ages worldwide in 2020

(Source: (Sung *et al*., 2021)).

Although it is generally agreed that the etiology of BC is complex and multifactorial, but dietary and lifestyle behavioural factors as well as environmental risk factors have been regarded as important risk factors associated with the pathogenesis of BC (Albuquerque *et al*., 2014; Dandamudi *et al*., 2018). Numerous non-modifiable risk factors such as age, genetic and reproductive-related factors are considered as important determinant factors on BC risk (Albuquerque *et al*., 2014; Sun *et al*., 2017). Early menarche, advanced age at menopause, and advanced age at first full-term pregnancy (FFTP), for example, are all variables that may raise the chance of developing BC (Kariri *et al*., 2017; Li *et al*., 2017). Apart from the non-modifiable factors, modifiable lifestyle factors such as dietary and lifestyle behavioral practices

are regarded as important modifiable risk factors associated with the pathogenesis of BC (Brown & Ligibel, 2018; Cicco *et al*., 2019). It is estimated that about 30 to 40% of cancers can be prevented through changes of modifiable lifestyle and environment risk factors throughout the lifespans (Friedenreich *et al*., 2021). Numerous studies have indicated that an unhealthy dietary practices, along with inactive lifestyle practices such as low physical activity level and high sedentary lifestyle (Brown & Ligibel, 2018; Friedenreich *et al*., 2021), alcohol consumption (Nagykálnai & Landherr, 2018) and smoking (Jones *et al*., 2017) have significantly increased the risk of BC. Numerous studies had documented on the role of several specific nutrients on the risk of BC such as vitamin D (VitD), folate, vitamin B6, and beta carotene as well as indole-3-carbinol, curcumin, sulforaphane, epigallocatechin gallate, piperine, quercetin and omega-3 fatty acids (ω3), display an anti-tumoral activity against BC and have the potential to offer a natural strategy for BC chemoprevention and reduce the risk of BC recurrence (Mokbel & Mokbel, 2019). Hence, an appropriate and healthy dietary habits and active lifestyle practices have essential impact on the prevention of BC risk among women (Boyle *et al.*, 2008).

Typically, oncological treatment procedures and regimens of BC patients are determined by the type and severity of the cancer's development stage. Common treatment options may include surgery, radiation therapy, chemotherapy, and molecular therapies. Depending on the type and also severity of BC stage, some patient might need only a single treatment option, but most patients may need to considered a combination of treatment, such as surgery with chemotherapy and/or radiation therapy (ACS, 2021a). Even though there are many kinds of cancer treatments accessible today, they are all accompanied by some adverse effects. For the majority of cancer types, chemotherapy is the most extensively used and successful kind of treatment

(Baldo & Pham, 2013). Initially, it was believed that chemotherapy medications would only kill cancer cells. However, it is now widely recognized that these drugs can also harm healthy cells, leading to dose-dependent side effects like diarrhea, vomiting, hair loss, mouth sores, and changes in weight or appetite (ACS, 2021a). These diverse side effects of cancer treatments might result in a number of medical issues that frequently necessitate hospitalization or even death (Muss, 2014).

It is clearly shown that cancer and its treatment exert wide ranges of disease and treatment-induced side effects that could significantly diminished nutritional intake and lead to unintentional weight loss and malnutrition (Malihi *et al*., 2013; Ryan *et al*., 2016). Some of the possible underlying causes associated with an increased risk of malnutrition and its adverse outcomes are the tumor's catabolic effects and abnormal metabolism of nutrients, inadequate intake attributed to tumor-induced anorexia, reduced food intake linked to treatment side effects like nausea, vomiting, stomatitis, constipation, and malabsorption, obstruction caused by the tumor or as a result of treatment and pain, anxiety, fatigue, or depression that increase the risk of improper dietary intake, and inactive lifestyle practices (Schueren, 2019). In general, active oncological treatment such as chemotherapy may negatively affect nutritional status (Boltong *et al.*, 2014) and quality of life (QoL) in patients with BC (Wu *et al.*, 2016). A deterioration of nutritional status is regarded as one of the common clinical manifestation found in cancer patients due to its cancer cachexia (Son, 2015). Cancer cachexia is a multifactorial wasting condition that results in increasing functional impairment and is defined by involuntary weight loss with continuing loss of skeletal muscle mass, either with or without loss of fat mass. Conventional dietary therapy is unable to totally restore this loss of mass (Prado *et al.*, 2016; Ryan *et al.*, 2016; Son, 2015). Cachexia is also defined as a body mass index (BMI) <20kg/m2, accompanied

by other three criteria namely, decreased muscle strength, fatigue, anorexia, low lean muscle mass index, increased levels of C-reactive protein or IL-6 and low serum albumin (Drescher *et al*., 2015) It is clearly to indicate that malnutrition and cachexia are significantly associated with poor disease and treatment outcomes (Baracos, 2018), impaired QoL, and worse overall prognosis (Baracos, 2018).

In recognition of nutritional and health impacts of cancer-associated with malnutrition risks, several evidence-based position papers and clinical guidelines have been published to prevent and reduce the adverse effects of cancer-associated malnutrition risk such as implementing a comprehensive nutritional screening and monitoring as well as nutritional interventions (Castillo-martínez *et al*., 2018). These nutritional risk screening and nutritional support are highly recommended and it should be incorporated into the treatment programs as early as possible and also throughout the patient treatment and care in order to reduce the incidence of malnutrition and its adverse outcomes (Arends *et al*., 2017a; Caccialanza *et al*., 2016). Nutritional care support during active oncological treatment has been regarded as an integral part of active adjuvant therapy on cancer care (Bicakli *et al*., 2018). Several nutritional care and support options can be implemented such as nutrition counseling with the possible use of oral nutritional supplements, enteral nutrition, or total or supplemental parenteral nutrition (Arends *et al*., 2017a; Caccialanza *et al.*, 2016). Nutritional intervention with dietitian counselling combined with the prescription of specific diet improved weight, muscle mass, and nutritional status by the PG-SGA in cancer patients receiving chemotherapy and reduce the malnutrition of these patients (Huong *et al*., 2021). It is well-documented that an adequate and proper nutritional intervention care and support given during the oncology treatments could exert the beneficial impacts on disease prognosis, patient QoL, efficacy of anti-tumor therapies,

and possibly prolong survival (Cicco *et al*., 2019; Gangadharan *et al*., 2017). Proper nutritional care such as healthy and balanced diet, regular physical activity and healthy weight management are regarded as important strategy to reduce the risk of malnutrition and its adverse effects associated with cancer metastasis and cancer-associated treatment as well as increase the survival rate (Cicco *et al*., 2019). All these could significantly improve the quality of disease treatment condition and preventing the worsening of disease progression. In fact, Numerous scientific evidences have shown that adequate intake of energy and essential nutrients such as ω3 (Liu & Ma, 2014), vitamins C, E,D, selenium and calcium (Greenlee *et al.*, 2014a; Harvie, 2014) are important and needed during the oncological treatment in order to support the oncological treatment response and to reduce the toxicity of pharmacological anti-cancer therapies used such as chemotherapy treatment (Arends *et al*., 2017a; Greenlee *et al.*, 2014a; Harvie, 2014).

Of all these nutritional support, oral nutritional supplements are commercially available homogeneous and usually nutritionally complete nutrient mixtures for oral consumption and are most often recommended to supplement volitional food intake (Arends *et al*., 2017a). In order to improve oral intake in malnourished cancer patients, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the Chinese Society for Parenteral and Enteral Nutrition (CSPEN) advise using oral nutritional supplements throughout therapy (Arends *et al*., 2017a). A good method of providing nutrition assistance is through nutritional supplements, which can boost the amount of protein, fat, carbohydrate, and vitamin content in food and offer a balanced supply of nutrients to suit the body's needs (Meng *et al.*, 2021).

One of the nutrients of concern, ω3 has been regarded as an essential nutrient used to support human health (Calder, 2018), it had been reported to play a role in the prevention of cardiovascular disease, diabetes, hypertension, inflammation, allergies, cancer and neural function (Aranceta & Pérez-Rodrigo, 2012; Sinclair, 2019). Studies have shown that ω3 could decrease the risk of BC and adverse events related to it (Khodarahmi & Azadbakht, 2014; Zheng *et al.*, 2013). In a systemic review of Zheng and his coworker (2013), it showed that intake of ω3 was associated with 14% reduction of risk of BC (Zheng *et al.*, 2013). The justification for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplements in BC patients was established by a number of cross-sectional studies that demonstrated a correlation between increased intake of these fatty acids and a lower risk of death from cancer (Bell *et al.*, 2014), but, specific human intervention studies are limited and the results have been variable (Mansara *et al*., 2015). Moreover, EPA and DHA are safe and have no cardiotoxic adverse effects, and they aid patients receiving radiation or chemotherapy in maintaining their body weight (Sánchez-Lara *et al*., 2014) and lessening the typical adverse effects of chemotherapy, like increased fracture risk, peripheral neuropathy, and loss of bone density (Hutchins-Wiese et al., 2014). (Hutchins-Wiese *et al.*, 2014). According to a small randomized pilot study, post-menopausal BC survivors undergoing AI therapy may experience decreased bone reabsorption while taking 4 grams of EPA and DHA daily (Hutchins-Wiese *et al.*, 2014).

VitD is a fat-soluble vitamin, and it presents in either ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3). It can be synthesized either endogenously in the skin after sunlight exposure and/or ingested from the diet source (Holick, 2013). VitD is important for the regulation of calcium and phosphates homeostasis in the body

(Chesdachai & Tangpricha, 2016; Chiang *et al*., 2017). A growing body of evidence has suggested that VitD metabolites in the body poses many important biological processes, including immune system modulation (Bizzaro *et al.*, 2017). For instance, it has been discovered that VitD controls the expression of genes implicated in the initiation and progression of cancer, either by promoting cell differentiation and death or by preventing cell proliferation, angiogenesis, invasion, inflammation, and the potential for metastasis (Feldman et al., 2014; Skrajnowska & Bobrowska-korczak, 2019). In addition, VitD insufficiency is seen as an adverse prognosis and is prevalent in BC patients (Vaughan-Shaw *et al*., 2017; Vrieling *et al.*, 2014; Yao *et al*., 2017). Several studies suggest that low VitD is associated with an incidence and mortality of several cancers (Wu *et al*., 2020). In a study of 2,177 postmenopausal BC patients, a significant increased risk of overall mortality among those BC patients with low circulating 25-hydroxyvitamin D (25(OH)D) concentrations (Vrieling *et al*., 2014). In addition, numerous studies have reported that VitD plays a role in controlling normal breast cell growth and has its capacity to stop the growth of cancer cells (Wulaningsih *et al*., 2016). In a cohort study of 1666 BC survivals in the United States, to assess the VitD status in relation to BC disease prognosis status, had showed that higher serum 25(OH)D had significantly associated with better disease prognosis (Yao *et al.*, 2017). Among premenopausal women, higher levels of 25(OH)D were associated with better overall survival, better BC specific survival, relapse free survival and invasive disease-free survival. In contrast, an inverse association was found between the concentration of 25(OH)D in the blood and tumor stage and tumor grade. These have highlighted that avoiding VitD deficiency is possibly an important preventive measures to reduce cancer incidence and improve cancer prognosis and outcome (Feldman *et al*., 2014; Yao *et al*., 2017; Skrajnowska & Bobrowska-korczak, 2019).

The beneficial effect of either ω3 and/or VitD supplementation on the cancer prevention have showed mixed results. In a nationwide randomized placebo-controlled trial in US using either VitD (2000 IU per day) and marine ω3 (1 g per day) for the median follow-up of 5.3 years on the cancer risk in adult men aged 50 years and above and women aged 55 years and above of age found that combined daily VitD or ω3 did not show significant beneficial effect on the risk of any invasive cancer compared to the control group (Manson *et al*., 2019a; Manson *et al*., 2019b). On the other hand, another meta-analyses study looking on the VitD supplementation and cancer incidence and mortality had reported that VitD supplementation decreased the risk of cancer mortality (Keum *et al.*, 2019; Y. Zhang *et al*., 2019) but did not decrease total cancer incidence (Keum *et al*., 2019). There was no proof that raising ω3 changed the incidence of cancer, according to a systematic evaluation of 10 RCTs comparing high to low ω3 intake for at least 6 months (Hooper *et al.*, 2006). A subsequent meta-analysis of RCTs increasing ω3 intake over at least six months found that supplementing with ω3 increased the risk of cancer by 10%, though this was not statistically significant (Zhang *et al*., 2014). This review did not stratify by supplementation level, did not analyze for specific cancer types, and only provided limited dosage information. Drawing from prior research findings, it appears that VitD and ω3 could offer a novel supplementary therapy by reducing inflammatory biomarkers and treatment resistance in BC patients. It is still unclear if co-supplementing with VitD and ω3 will be beneficial following a BC diagnosis. Thus, the purpose of this research is to examine how co-supplementing with vitamins D and ω3 affects inflammatory biomarkers and nutritional status in BC patients.

1.2 Problem statement

BC is the most frequent malignancy among women in both developed and developing countries (Baburin *et al.*, 2016; Enayatrad *et al*., 2016; Ibrahim et al., 2014). According to Sung et al. (2021) (Sung *et al*., 2021), it is the primary cause of cancer-related fatalities in women worldwide, accounting for one in six cancer-related deaths. It is also the fifth most prevalent cause of cancer-related deaths globally (Ferlay *et al.*, 2013; Sung *et al.*, 2021). In Palestine, BC has emerged as the most prevalent cancer with 934 cases reported in 2022, with incidence rate was 37.4 case per 100,000 female population (MOH Palestine, 2022).

Common clinical manifestation of cancer patients such as cancer cachexia and rapid weight loss are often reported among patients with BC, especially in advanced stage, which could be aggravated during and/or after active oncological treatment such as chemotherapy. Loss of weight is associated with unfavourable oncologic outcomes, such as a higher risk for toxicity and shorter length of survival (Dechaphunkul *et al.*, 2013). Although it is generally agreed that proper and adequate nutritional intervention care is an important approach to be incorporated into the oncology treatment to minimize and reduce the risk of progression and/ or recurrence of BC (El-hissi *et al*., 2016; Gangadharan *et al*., 2017). Similarly for the patients during oncology treatment, it has been shown that appropriate nutrition, such as increases in the quantity and quality of food consumed, may support healing, recovery, and BC survival (Milliron *et al*., 2014). Women diagnosed with early-stage BC may fare better overall if they adopt healthy eating habits that emphasize a high intake of fruits, vegetables, whole grains, poultry, and fish, rather than following the western diet pattern that emphasizes refined grains, sweets, high-fat dairy products, red and processed meats, and refined grains. (Kwan *et al*., 2009). Daily Intake of ω3 has been used to minimise and to

prevent the worsening nutritional state of patients during oncology treatment. Numerous studies of ω3supplementation among patients with BC, who had supplemented with 2.5 g/d ω3 showed a beneficial effect on body weight compared to those didn't take supplements(Aredes *et al.*, 2019). Despite an increasing amount of research highlighting the advantages of ω3 supplementation, few human clinical trials have been conducted (Aredes *et al.*, 2019). Similarly for VitD, it is found to have protection against inflammatory diseases and immune-mediated disorders by inhibiting adaptive immunity and enhancing innate immunity (Berti *et al.*, 2017). VitD deficiency has been reported in many populations across the lifespans, even populations living in the sunny countries like in Palestine (Harinarayan et al., 2013; Lopes et al., 2017). Hence, it is crucial to identify and fully comprehend the optimal health roles of ω3 and VitD supplementation, especially in improving nutritional status and health outcomes, particularly among vulnerable populations like oncology patients. However, evidence in this area remains limited. This need is especially critical for populations facing significant health burdens, such as in Gaza, where BC prevalence is high, and the healthcare system is challenged by financial constraints and limited resources. In this context, understanding the interplay of unique environmental, dietary, and lifestyle factors that influence BC progression and management becomes imperative. A particularly pressing issue is the high prevalence of vitamin D deficiency in Gaza, a paradox given its sunny climate. This deficiency is likely exacerbated by socio-environmental conditions such as limited outdoor activities due to cultural or safety concerns, poor dietary intake, and restricted access to healthcare resources. These factors exacerbate the vulnerability of BC patients, who may already suffer from compromised nutritional status. Addressing these deficiencies has the potential to yield substantial health benefits, particularly for this underserved

population. Research in such settings is vital for uncovering how these factors, combined with limited healthcare infrastructure, shape the experiences and outcomes of BC patients. This knowledge can inform the development of targeted interventions and policies to address the specific needs of women in Gaza and other resource-constrained regions. Further clinical trials and research are necessary to gain a comprehensive understanding of the full spectrum of health benefits associated with ω3 and VitD supplementation, particularly within the framework of oncology treatment and management. These efforts could significantly improve patient care strategies and outcomes for vulnerable populations globally.

1.3 Significance of the study

The idea of nutritional support as a component of an all-encompassing cancer management plan has drawn more and more attention during the past 20 years (Bicakli *et al.*, 2018). There is scant evidence linking the major food groups to a higher risk of BC. Some evidence suggests nutritional intervention as a key factor in determining cancer prognosis, patient nutritional status and QoL and, notably, efficacy of anti-tumor therapies. Diet, exercise, and weight control do, in fact, significantly improve survival for BC patients. Women undergoing active oncology treatments such as chemotherapy are highly affected by adverse changes in body composition, with frequent sarcopenia, accompanied with excessive gains in body fat, a significant risk factor for development of comorbidities such as cardiovascular diseases and diabetes, thus influencing long-term survival (Bicakli *et al.*, 2018; Bozzetti, 2015; Ihara *et al*., 2019; Tan *et al*., 2015). Therefore, proper and adequate nutritional intervention should be incorporated as an integral part of the multimodal therapeutic approach to prevent

and reduce the risk of recurrence, mortality, and development of cancer (Cicco *et al*., 2019).

In Palestine, nutritional intervention strategies in oncology settings, particularly for patients undergoing chemotherapy, are poorly evaluated, limiting the ability to make effective recommendations for this population. Appropriate nutritional supplementation and intervention have the potential to improve nutritional status, reduce mortality, and enhance QoL among these patients. Moreover, effective nutritional strategies can slow disease progression and reduce recurrence, making them a critical step in alleviating the health burden, especially in low- and middle-income countries with fragile healthcare systems. Despite this, few studies have specifically focused on newly diagnosed patients or those in resource-limited settings like Gaza. To address these gaps, my study is designed to implement a structured supplementation regimen, targeting newly diagnosed patients. It examines both nutritional status and inflammatory markers, providing a comprehensive understanding of the effects of supplementation in this unique context. By doing so, the study aims to contribute valuable insights that could inform tailored interventions and policies to support oncology patients in similar low-resource environments.

1.4 Research questions

i. Are there any significant effects of the ω3 and/or VitD supplementation for nine weeks on dietary intakes, nutritional status, QoL, and inflammatory biomarkers among BC women undergoing chemotherapy treatment?

ii. Is there any significant effect of the ω3 and/or VitD supplementation for nine weeks on dietary intake markers among BC women undergoing chemotherapy treatment?

iii. Is there any significant effect of the ω3 and/or VitD supplementation for nine weeks on nutritional status among BC women undergoing chemotherapy treatment?

iv. Is there any significant effect of the ω3 and/or VitD supplementation for nine weeks on QoL among BC women undergoing chemotherapy treatment?

v. Is there any significant effect of the ω3 and/or VitD supplementation for nine weeks on inflammatory biomarkers among BC women undergoing chemotherapy treatment?

1.5 Objectives

1.5.1 Main objective

To determine the effect of nine weeks of combined ω3 and VitD co-supplementation on dietary intakes, nutritional status, QoL, and blood inflammatory markers among BC women undergoing chemotherapy treatment in the Gaza Strip, Palestine.

1.5.2 Specific objectives

1. To assess the effect of nine weeks of the ω3 and/or VitD supplementation on dietary intakes among BC women undergoing chemotherapy treatment.
2. To assess the effect of nine weeks of the ω3 and/or VitD supplementation on nutritional status among BC women undergoing chemotherapy treatment.
3. To assess the effect of nine weeks of the ω3 and/or VitD supplementation on QoL among BC women undergoing chemotherapy treatment.
4. To assess the effect of nine weeks of the ω3 and/or VitD supplementation on blood inflammatory markers among BC women undergoing chemotherapy treatment.
5. To compare the effect of nine weeks of combined ω3 and VitD co-supplementation, ω3 or VitD supplement alone and control on dietary intakes, nutritional status, QoL, and blood inflammatory markers among BC women undergoing chemotherapy treatment.

1.6 Research hypotheses

First Null hypothesis

There is no significant effect on dietary intakes, nutritional status, QoL, and inflammatory biomarkers between control, VitD supplementation alone, ω3 supplementation alone and combined ω3 and VitD co-supplementation groups among BC women undergoing chemotherapy treatment in the Gaza Strip, Palestine.

Alternative hypothesis

It is hypothesizing that there is a significant effect on dietary intakes, nutritional status, QoL, and inflammatory biomarkers between control, VitD supplementation alone, ω3 supplementation alone and combined ω3 and VitD co-supplementation groups among BC women undergoing chemotherapy treatment in the Gaza Strip, Palestine.

Second Null hypothesis

There is no significant the effect of the ω3 and/or VitD supplementation on dietary intakes among BC women undergoing chemotherapy treatment.

Alternative hypothesis

There is a significant the effect of the ω3 and/or VitD supplementation on dietary intakes markers among BC women undergoing chemotherapy treatment.

Third Null hypothesis

There is no significant the effect of the ω3 and/or VitD supplementation on nutritional status among BC women undergoing chemotherapy treatment.

Alternative hypothesis

There is a significant the effect of the ω3 and/or VitD supplementation on nutritional status among BC women undergoing chemotherapy treatment.

Fourth Null hypothesis

There is no significant the effect of the ω3 and/or VitD supplementation on QoL among BC women undergoing chemotherapy treatment.

Alternative hypothesis

There is a significant the effect of the ω3 and/or VitD supplementation on QoL among BC women undergoing chemotherapy treatment.

Fifth Null hypothesis

There is no significant the effect of the ω3 and/or VitD supplementation on blood inflammatory markers among BC women undergoing chemotherapy treatment.

Alternative hypothesis

There is a significant the effect of the ω3 and/or VitD supplementation on blood inflammatory markers among BC women undergoing chemotherapy treatment.

1.7 Conceptual framework of the study

Figure 1.2. illustrates the conceptual framework used to describe and assess the effect of combined ω3 and VitD supplementation on several important clinical outcomes of the topic of interest namely, nutritional status, QoL, inflammatory markers and dietary intakes in BC women that were undergoing active chemotherapy treatment, in comparisons of single ω3 or VitD supplementation alone on these outcomes.

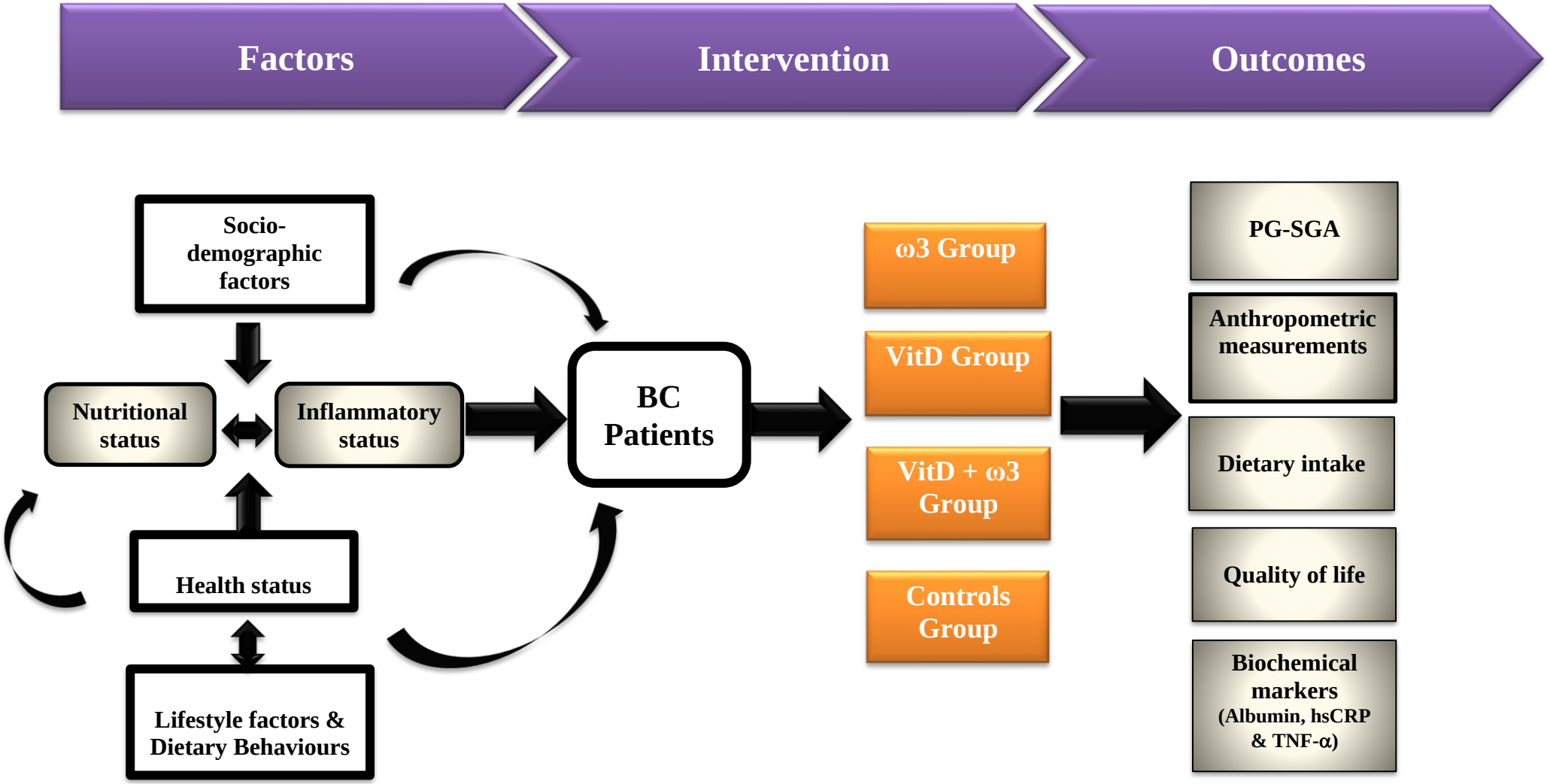


Figure 1.2 Conceptual framework of the study

1.8 Operational definition

Breast cancer

A disease that affects the breasts when certain breast cell types develop abnormalities and begin to proliferate out of control. The tumor may expand and infiltrate surrounding tissue, or the cells may separate and infiltrate the bloodstream or lymphatic system, posing a threat to other organs (Odeh, 2011).

Breast cancer stage

Characteristics of breast tumors at the time of diagnosis, such as stage, size, and nodal status (Oeffinger *et al.*, 2015).

Omega-3 fatty acids

An essential polyunsaturated fatty acids, as defined by a double bond at the third carbon from the methyl end of the carbon chain, is highly required for humans (Burdge *et al*., 2002).

Quality of life

An overall enjoyment of life as defined by National Institutes of Health, while Center for Disease Control and Prevention defined it as, a person or group's perceived physical and mental health over time (Post, 2014). The QoL of cancer patients is determined by the impact on their well-being of their social (social activities, being helpful, body image, anxiety, and depression), psychological (life satisfaction, need for social support, and role function), and physical (movement, physical activities, and

ability to succeed in work and family responsibilities). Pain, difficulty breathing, nausea, baldness, impotence, and, of course, the side effects of the same are signs of the disease and therapy (Rodríguez, 2013).

C-reactive protein (CRP)

It functions as a sensitive marker of systemic inflammation, synthesized by the liver. It has historically been used to detect acute injury, infection, and inflammation as a nonspecific acute-phase reactant. Its main use has been in the assessment of low-grade inflammation (Dossus *et al.*, 2014; Fernandes *et al.*, 2016).

Tumor necrosis factor-alpha (TNF-α)

It is a critical cytokine that is produced chiefly by macrophages in response especially to endotoxins, plays a key role in mediating inflammation and contributes significantly to both physiological and pathological processes (Chu, 2013).

CHAPTER 2

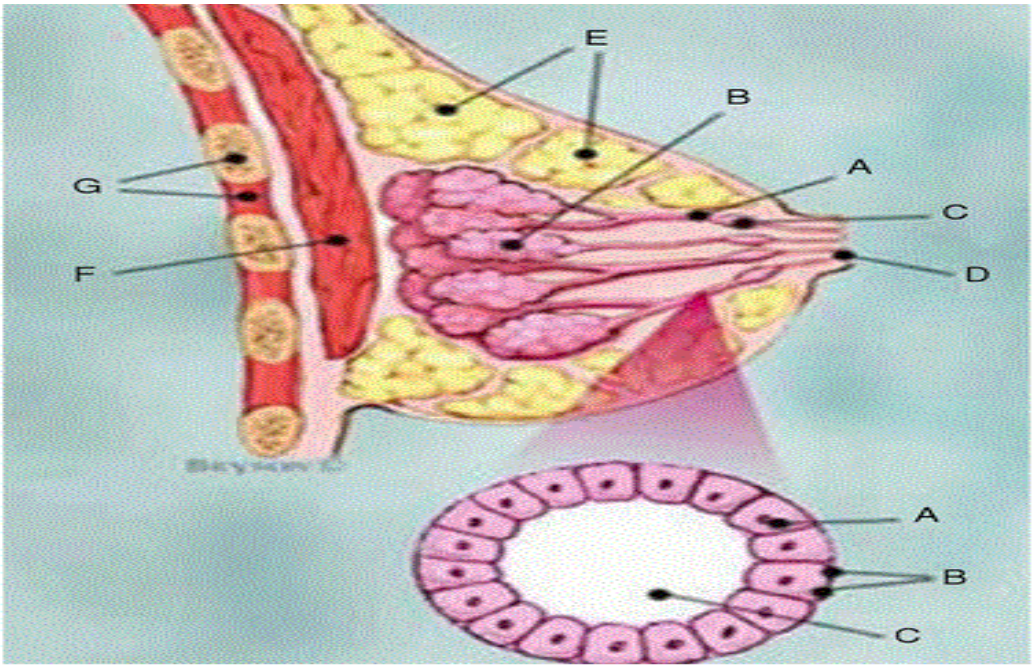
LITERATURE REVIEW

2.1 Overview of breast anatomy

The anterior chest wall supports the breast. Between the second and sixth ribs along its longitudinal axis is the base of the breast. Every woman's breasts have a comparable internal structure (Ali, 2016). However, a number of factors, including age, race, diet, female parity, and menopausal state, affect its size and shape status (Darlington, 2015). Fat, connective tissue, and glandular tissue, the latter of which is the functional component of breast tissue, make up the female breast's basic composition (Ali, 2016).

Each breast's glandular tissue is separated into 15 to 20 lobes, each of which has tubular structures like trees that branch out from the nipple. There are 10–100 alveoli in each lobe, which are where hormones and milk are made (McDonald, 2015). Ducts carry milk from the alveoli to the nipple, influenced by reproductive hormones. The nipple comprises epithelial, glandular, erectile, and nervous tissues and is encircled by the darker area known as the areola (Darlington, 2015). The breast's functional unit is called the terminal ductal lobular unit. The percentage of glandular tissue in the breast is known as breast density (McDonald, 2015; Williams et al., 2021). Glandular tissue is one type of highly modified and specialized sweat gland. It changes with age and reacts to hormones in the body (Gilbert & Slingerland, 2013; Williams *et al.,* 2021). Tissues that are fat or connective are regarded as supporting tissues for the anatomy of the breast. There are two distinct forms of connective tissues found in the breast: The tissue that spans between the lobules and holds the breast tissue together is called interlobular connective tissue. A specific kind of connective tissue that surrounds the terminal ductal lobular unit is called intralobular connective tissue. Mammary glands contain breast fat

tissues that are implanted in them. (Gilbert & Slingerland, 2013; Williams *et al.*, 2021). During puberty and lactation, reproductive hormones play a crucial role in the development of the breasts. Progesterone encourages the growth of cells that produce milk, whereas estrogen encourages the creation of glands and ducts. Oxytoxin is the cause of the milk ejection from the nursing breast, while prolactin is the hormone that encourages milk production (Odeh, 2011).



A Lactiferous duct
B Lobules
C Cross section of lactiferous duct
D Nipple
E Adipose tissue
F Pectoralis major muscle
G Chest wall / ribs
H Cooper's ligaments

Figure 2.1 The breast's interior anatomy

(Source: Darlington, 2015)

2.2 Breast cancer

BC is commonly understood to be an uncontrollably changing breast tissue that primarily forms lumps. A breast tumor is this mass, and it has the ability to invade nearby tissues or spread (metastasize) to other parts of the body. When BC cells proliferate, they often do so to lymph nodes in the underarms and above the collar bone (CDC, 2023).

2.2.1 Worldwide trend of breast cancer

With estimated 2.3 million new cases, or 11.7% of all cancer cases, BC now surpassed lung cancer as the primary cause of cancer incidence worldwide in 2020 (Sung *et al.*, 2021). It stands as the fifth most common cause of cancer-related deaths globally, claiming 685,000 lives (Ferlay *et al.*, 2013; Sung *et al.*, 2021), with 685,000 deaths. Among women, BC holds the highest frequency of diagnosis, accounting for 30% of all cases (Siegel & Miller, 2019), and ranks as the foremost cause of cancer-related fatalities, claiming approximately 15.5% of total cancer deaths. Notably, it followed by lung and colorectal cancer in mortality, contributing to one in six cancer-related deaths (Sung *et al*., 2021). Furthermore, BC ranks first in incidence across the majority of countries (159 out of 185) and leads in mortality in 110 nations. Exceptions exist, particularly regarding mortality, where lung cancer precedes BC in Australia/New Zealand, Northern Europe, Northern America, and China, while cervical cancer takes precedence in numerous countries in sub-Saharan Africa (Sung *et al.*, 2021).

Globally, BC incidence rates rose sharply in several Northern American, Oceanian, and European nations during the 1980s and 1990s. This increase was probably caused by shifts in the prevalence of risk factors as well as increased detection from the widespread use of mammography screening. Then, in the early 2000s, there