Special Issue: Maturitas
Health and wellbeing after cancer

Breast cancer and exercise: the role of adiposity and immune markers

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ABSTRACT

Currently, breast cancer forms a quarter of all cancers and 15 % of cancer-specific deaths amongst females. The global occurrence of breast cancer has increased in the last decade whilst the mortality rate has decreased. Exercise can be beneficial to breast cancer patients through changes of adiposity and immune responses. Even though there is some evidence supporting the improvement of fat metabolism and immune function after an exercise program in breast cancer, randomized controlled studies are limited and require further comprehensive analysis in this population group. Herein, we identify the known effects of exercise programs on adiposity and immunological markers which can improve breast cancer outcomes.

Keywords:
Breast cancer
Exercise, Biomarkers
Adiposity
Immune biomarkers
Breast cancer outcome

1. Introduction

Breast cancer leads to physical and mental distress [1] which is linked with increased prevalence of malignancy-related mortality amongst females worldwide [2]. The World Health Organization [3] mandates that exercise improves physical and mental wellbeing in general and that consistent moderate-intensity exercise decreases the risk of cardiovascular disease, diabetes and cancer. Interestingly, exercise programs for breast cancer have been reported to contribute to positive outcomes with increased survival rates [4]. This article gives an overview of the current trend for global breast cancer, possible risks factors and the benefits of exercise programs on breast cancer prevention and outcomes, with specific emphasis on adiposity and immunological biomarkers. It has been shown that certain biomarkers are improved with physical activity; for example, adipokines, estrogen, insulin resistance, C-reactive protein [5,6], T helper (Th) cells [7] and cytotoxic activity of NK cells [8]. These biological changes following exercise training have been associated with improved breast cancer outcomes and reduced mortality rates [6].

2. Methodology

This review article summarizes the existing knowledge of the benefits associated with exercise on breast cancer outcomes through adiposity and immunological mechanisms using related articles published between 2000 and 2017 in Medline and PubMed. The key terms of this review consists of breast cancer OR breast neoplasms AND exercise OR physical activity, breast cancer OR breast neoplasms AND biomarkers for adiposity OR obesity-related biomarkers, breast cancer OR breast neoplasms AND immunological biomarkers.

3. The global incidence of breast cancer

Breast cancer is one of the leading health issues of women worldwide. Currently, breast cancer is ranked as the most common diagnosed cancer with an estimated 1.7 million cases and over 520,000 deaths worldwide [9]. It accounts for one quarter of all cancer types and 15 % of all cancer related deaths in females. The higher developed countries such as USA, Europe (northern and western), Australia and New Zealand have higher incidence rates of breast cancer as compared to the intermediate developed countries of Europe (central), Latin America and the Caribbean; the

lowest incidence rates of breast cancer being in low developed countries, Africa and Asia [10]. However, the highest death rate is observed in parts of Africa and South Asia [11], with the death rate being lowest in USA, Europe (northern and western), Australia and New Zealand [11]. Data from the World Health Organization shows that the occurrence of breast cancer has increased rapidly in 22 of 39 observed countries between 2008 and 2012, whilst the global mortality rate has decreased [11].

3.1. The incidence trends by age

In the 1980s, the incidence of breast cancer dramatically increased in US women aged over 40 years [12]. This may have resulted from improvements in mammography screening. The incidence remained constant for women who were in their 40s through the 1990s but gradually increased in women above 50 [12]. This upward trend is likely due to increased rates of obesity in older women and the use of hormonal replacement therapy (HRT) to alleviate menopausal symptoms [13]. In the early 2000s, following the publication of the Women's Health Initiative study [14] the incidence rate decreased in women aged over 50, possibly due to the decreased use of HRT. The incidence of breast cancer has been reported as stable for US women in their 40s and 50s, although an increase by 1-1.2 % annually is noted in women aged 60-70 years. For women aged in their 40s, the incidence rate of breast cancer has been stable since 1986, whereas for women aged between 20-39 years the incidence rate increased by 0.6 % per annum from 1994-2012 [12].

3.2. The incidence trends by race and ethnicity

The incidence and mortality rates of breast cancer in relation to race and ethnicity in the US suggests that non-Hispanic women have a higher incidence (128.1 (white) and 124.3 (black) / 100,000) than Alaska native/American Indian (.rate??.), Hispanic (91.9/100,000) and Asian Pacific women (88.3/100,000) [12]. Even though, the incidence rate in white women is slightly higher than black women, the mortality rate in black women is 42 % higher than in white women [12]. The lower incidence of breast cancer in Alaska native/American Indian, Hispanic and Asian Pacific women may represent the variation in the risk factors associated with decreased risk, ie. younger age having their first child and breast feeding for over 12 months [12].

4. Risk factors of breast cancer

The presence of risk factors does not denote that a woman will develop breast cancer, just as the absence of risk factors does not necessarily prevent breast cancer [15]. However, it is very important for a woman to understand her risks for breast cancer and undertake specific interventions to reduce the risks includingbreast cancer screening [15]. Known risk factors are strongly associated with ageing, reproductive history, exogenous hormone exposure and family history [15]. Indeed, some risk factors can be controlled but others are difficult to manage. The possibility of breast cancer in American women dramatically increases every 10 years. For example, the breast cancer risk of a woman aged 30 is 0.44 %, whereas a woman aged 70 has a risk of 3.89 % [12]. Some data suggests that the impact of lifestyle and reproductive patterns are on the upward trend for breast cancer incidence; for instance, agricultural countries changing to industrial societies [16], menarche at younger age and menopause at a later age [17]. In addition, the use of HRT in pre- and post-menopause [15], the use of oral contraceptives and having a first full-term pregnancy at a later age, are linked to rising breast cancer occurrence [15, 18, 19]. Females that are periparous or multiparous at a younger age, have a lower relative risk of breast cancer at or after menopause compared to nulliparous women [17]. Interestingly, women who breast-fed have a hazard ratio of 0.75 for premenopausal breast cancer compared to women who never breast-fed; although this phenomenon is associated to those with a family history of breast cancer [20]. Moreover, the presence of BRCA1 and BRCA2 gene mutations are associated with higher risk of breast cancer [21]. As a consequence, counselling and timely screening procedures are provided to women who carry these genetic mutations [21].

In the last decade research studies have alluded to chronic low grade inflammatory responses being one of the major contributing factors leading to chronic diseases such as diabetes, cardiovascular disease and cancer. One of the major culprits of low grade inflammation is obesity [22]. In fact, in obese animals there is a correlation between adipocyte hyperplasia and tumor progression [23]. It is likely that in obesity, poor functional adipose tissue secretes higher levels of pro-inflammatory factors that inhibits the release of adiponectin. This alteration may explain the link between obesity, type-2 diabetes, metabolic syndrome and cancer [23].

4.1. Breast cancer and obesity

Obesity is likely to be associated with increased risk of breast cancer, especially in postmenopausal women [24]. For every 3.2 kg gained over the age of 18 the risk factor for breast cancer increases with an estimated relative risk of 2.85, increasing their mortality rate by 7 % [25]. This attribute can be related to several mechanisms through the increase of adiposity, including increased blood levels of estrogen, insulin and insulin-like growth factors (IGF) [26] as well as endocrine disrupting compounds (organic pollutants), such as, organochlorines which accumulate and are stored in fatty tissues, including that of adipose mammary tissue [27]. In addition, adipokines and leptin, produced and secreted by adipocytes, are higher in obese individuals and may contribute to postmenopausal breast cancer [6]. Moreover, the association between obesity and activation of immune cells (M1 macrophages, B cells, T cells), chemokines, pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and pro-angiogenic factors, change the body milieu contributing to increased risk of breast cancer [28].

5. Effects of exercise on overall health and disease prevention

The ancient Greek physician, Hippocrates, stated in the 5th century BC that if individuals lack their energy expenditure, they would be liable to disease, deteriorated growth and quicker ageing [29]. The observational studies conducted between 1940 and 1950 noticed that workers who were more active, such as bus conductors, had lower incidence of heart disease than bus drivers [30]. Exercise training reduces the precedence of some chronic diseases due in part to its effects on anti-inflammatory processes [31]. Regular and long term moderate aerobic exercise enhances fat metabolism which results in the reduction in adipokine secretion [31]. Physical activity has been shown to decrease IL-6, IL-8 and IL-15 cytokines, whereas IL-1 receptor antagonist and soluble TNF-alpha receptor which are increased during muscle contraction, may contribute to anti-inflammatory processes [32]. Likewise, a 10 week combined walking and weight training program dramatically reduced C-reactive protein in hypercholesteremic people with inactive lifestyles [33].

WHO recommends that an active lifestyle improves overall health in adults aged 18-64 years, includes that of leisure physical activity (gardening, walking, dancing, swimming), transportation (cycling, walking), occupational (work), household tasks and contributing to game play, sports or planned exercise. This leads to improved heart function, muscular fitness and bone health, as well as contributing to reduced risk of developing chronic disease [34]. Generally, an adult should partake in at least 150 minutes of moderate intensity aerobic activity or at least 75 minutes of vigorous intensity aerobic activity per week [34]. A prospective cohort study of 3,918 subjects conducted in England between 1990 and 2014 reported that the mortality rate of people who lived sedentary lifestyles was highest at approximately 42/1,000 persons per year risk (PYR) and lowest amongst those who met the recommended activity levels, at approximately 6/1,000 PYR. Hence, activity reduced the mortality rate by 25 % [35] and strategies to involve the general population in engaging in an active lifestyle should be emphasized for public health promotion [35].

5.1. Effects of exercise on immunological parameters

Acute exercise releases the stress hormone cortisol which upregulates monocyte chemokine receptor type 2 (CCR2) expression mediating monocyte infiltration in inflammatory diseases, including that within the tumor site. In addition, upregulation of the major histocompatibility complex (MHC) class II expression, IL-12 production, neutrophils and natural killer (NK) cells, have been noted in the circulation during bouts of acute exercise [36]. In addition, a short bout of heavy cycling increases pro- and anti-inflammatory responses, including cytokines (TNF-alpha, IL-6 and IL-4), T cells, B cells, monocytes and growth factors [37]. Likewise, immediately following brief exercise, gene expression of some monocytes involved in vascular diseases such as in asthma and arthritis are altered [36]. More specifically, a single bout of vigorous exercise at approximately 80 % VO_2max alters the expression of a number of NK cell genes which are involved in cancer prevention [36]. These findings suggest that exercise may contribute to chronic disease prevention via the innate immune system. Moreover, long term exercise and/or high-intensity training in young swimmers exhibits greater leukocyte transcriptional changes in some genes which are related to mitochondrial energetics and protein production, as well as downregulating genes that are involved in inflammation [38].

6. Epidemiological studies linking exercise with the incidence of breast cancer

Physical activity in adulthood tends to reduce the risk of breast cancer. In a systematic review and meta-analysis study, associating physical activity to chronic disease outcomes between 1980-2016, there was a strong correlation between those who achieved total physical activity several times higher than the recommended minimum to the risk of five chronic diseases including, breast cancer, colon cancer, diabetes, ischemic heart disease and ischemic stroke events. Thirty five prospective cohort studies (involving 50,949,108 cases of breast cancer) reported a 14 % reduction in the risk of breast cancer for those in the highly active category (over 8,000 metabolic equivalent (MET) minutes/week) with relative risk of 0.863 [39]. Exercise appears to reduce the risks of breast cancer through a number of mechanisms including reducing body fat which in turn reduces estrogen and insulin concentrations. Indeed, these biological substances have mitogenic effects on mammary cells [6]. Likewise, leptin released from adipose tissue, which has been associated with post-menopausal breast cancer, significantly decreases following aerobic activity [6]. Therefore, exercise may have positive effects in reducing the incidence of breast cancer, by improving the immune system. Indeed, exercise has been shown to increase circulatory NK cells by 5-fold which play a key role in the defense against pathogens and cancer immune-surveillance [36]. Moreover, there is evidence to suggest that physical activity during adolescence or young adulthood may lower the risk of pre-menopausal and post-menopausal breast cancer [40]. Overall, the decreased risk of breast cancer associated with physical activity differs according to age; 16 % for adolescence, 8 % for early adulthood, 15 % for middle adulthood and 17 % for over the age of 50 [41]. Importantly, breast cancer prevention efforts must start from the early stages of a woman's life [16].

A prospective cohort study in 78,733 women conducted between 1997-2011 [42], assessed the degree of physical activity during adolescent and adult life. It was noted that moderate physical activity in women aged 14-22 reduced the risk of pre-menopausal breast cancer considerably. High intensity physical activity in these young women (over 4,320 MET minutes/week) showed a modest correlation with breast cancer risk reduction. The association is likely stronger in breast cancer patients with estrogen receptor negative tumors and in younger pre-menopausal women. However, there was no correlation between physical activity in early life to the risk of developing post-menopausal breast cancer [42]. The likely mechanism involved in reduced breast cancer risk for an adolescent who regularly performs exercise could be due to delayed onset in menarche and/or reduced menstrual cycles, shortening reproductive hormone exposure [43].

6.1. Exercise as an adjuvant therapy following breast cancer diagnosis

Physical activity, especially moderate intensity aerobic exercise for females following breast cancer diagnosis, has been noted in a number of studies to be advantageous in regards to breast cancer outcomes, decreasing the mortality rate by >30 % [4] and decreasing recurrence rates. As a result of exercise, total body fat reduces, as well as a number of inflammatory biomarkers which could contribute to better outcomes in patients with breast cancer [47]. Likewise, in a cohort-longitudinal study, it was clear that fast walking (3 hours/week) prior to and following breast cancer diagnosis in postmenopausal women reduced the mortality rate by 40 % [44]. In addition, an aerobic exercise regime prescribed to women with breast cancer during early treatment in the Netherlands between 2010-2013, reduced fatigue and increased overall fitness [1]. Furthermore, sleeping disturbance, mood disturbance and anxiety declined following a 12 week aerobic exercise program in Thai women undergoing adjuvant chemotherapy [45]. Most importantly, reports in previous systematic reviews, suggested that aerobic exercise with moderate-high intensity (50-85 % of maximal heart rate), 3 times/week ranging between 8-24 weeks, to be the most frequent mode for breast cancer patients and survivors as this program may also have a positive effect on the cardiovascular, muscular and neurological systems. As a consequence this can lead to improvements in quality of life, such as the ability to deal with daily tasks [46]. Improvements in clinical outcomes in breast cancer patients following different exercise regimes are shown in Table 1. Although the American College of Sports Medicine has identified safety and benefits of exercise programs to breast cancer outcomes, there are a limited number of randomized controlled trials that have assessed the positive effects of exercise to breast cancer outcomes. Hence, the need for clarity on the mechanisms that may be related to exercise and cancer prognosis [47].

6.2. Effect of aerobic training on obesity-related cancer risk biomarkers in breast cancer

Obesity is an important contributing factor to the generation of low grade chronic inflammation leading to chronic conditions, including metabolic diseases, immune dysfunction and cancer; as a result of improper fat metabolism [22]. This condition however, can increase the recurrence and mortality rates of breast cancer survivors [48]. Adipose tissue produces high levels of pro-inflammatory cytokines (IL-1, IL-6, TNF-alpha) and monocyte chemo attractant protein, which are known to be associated with insulin resistance [49]; an adverse effect well known for mammary cell proliferation [5]. However, further randomized clinical trials are required in order to ascertain appropriate exercise regimes on adiposity that may influence breast cancer survival [47].

In a systematic review it was clear that alterations in adiposity related biomarkers, including body mass index (BMI), leptin, adiponectin, sex hormone binding globulin (SHBG), estrogen, androgen, insulin resistance, IL-6, TNF-alpha and C-reactive protein (CRP), as a result of physical activity, are likely to lower the risk of postmenopausal breast cancer [5]. In addition, long term exercise has been shown to decrease estradiol levels and increase SHBG in postmenopausal women who reduced more than 0.5 % of body fat [50]. In addition, exercise reduces testosterone levels by decreasing adiposity or by increasing SHBG [51], as well as improving insulin sensitivity, reduces adipokines and CRP which directly influence the risk of breast cancer [5].

Furthermore, a 10-year prospective cohort study involving 603 breast cancer patients [52] showed levels of insulin to be strongly associated with C-peptide levels which leads to a higher mortality rate for breast cancer in post-menopausal women. Insulin levels were also associated with waist-hip ratio and BMI, and negatively correlated with SHBG levels. However, there was no relation between leisure-time physical activity and mortality rate [52].

In a randomized clinical trial, obese women (BMI $\geq$25 kg/m^2) in the early stages of breast cancer , underwent a program which included 3 weekly supervised sessions of moderate-intensity (65-85% estimated VO_2max) aerobic exercise and a hypocaloric eating program. The study showed a reduction in body weight, waist-hip ratio and resting diastolic blood pressure after 6-months of intervention [53]. As a consequence, decreased leptin and total cholesterol levels were also noted.

The decreased body weight and waist circumference were associated with a reduction in CRP. These biological markers are likely to have a positive outcome to the mortality and overall health outcomes to patients with breast cancer [53]. In a 6-month counselling program (face to face and telephone) for breast cancer patients with obesity, a recommended daily caloric intake of 1,200-2,000 kcal combined with a home-based physical activity program (150 mins/week of moderate intensity) significantly reduced body weight and waist-hip circumference compared to patients who received only usual care [54]. Those patients who lost > 5% of body weight also showed decreased levels of leptin, insulin, IL-6 and CRP [54]. These biomarkers are hypothesized to decrease the risk and mortality of breast cancer [55]. Moreover, a 12-month weight training regime reported to be a safe exercise program for breast cancer survivors resulted in decreased body weight, percent body fat and insulin growth factor levels [56]. However, further randomized trials are required to assess the benefits of reducing weight in obese breast cancer survivors to prevent breast cancer recurrence. Weight management strategies especially the optimal exercise program and diet control are required to understand the mechanisms which are beneficial for survival outcomes [57].

6.3. Effect of exercise on the immune biomarkers in breast cancer

Aerobic exercise activity has been shown to improve immunological biomarkers in breast cancer patients [58], although there are no reports showing improvement in inflammation and immunological markers in breast cancer patients during chemotherapy or radiation treatment. In fact, chemotherapy used to treat breast cancer decreases the number of B and T cells suppressing overall the immune system [59]. In a 6 month moderate aerobic exercise regime in breast cancer patients after completion of chemotherapy, there was an improvement in T cell recovery by increasing the percentage of CD4+ CD69+ T cells. In addition, in a randomized controlled trial, a 15 week moderate-high intensity exercise regime (70-75 % VO_2max) in postmenopausal breast cancer patients, increased the cytotoxic activity of NK cells which should be beneficial to overall survival [8]. A previous study noted that the cytotoxic activity of NK cells was significantly higher in tumor-free survivors compared to those who had tumor-related mortality [60]. Interestingly, vasoactive intestinal peptide (VIP), an autocrine growth factor regulating cell proliferation, survival and differentiation in human breast cancer cells is blocked by the generation of natural anti-VIP antibodies stimulated by regular exercise. As a consequence, exercise programs may be important to prevent breast cancer recurrence [61].

Furthermore, a twelve-week aerobic exercise training (home-based exercise) in breast cancer survivors reduced pro-inflammatory cytokines and epithelial neutrophil activating protein levels (angiogenesis and apoptosis related markers). This suggests that aerobic exercise program is likely related to angiogenesis and apoptosis which may be beneficial to cancer prognosis [62]. A single bout of strenuous exercise such as a half marathon reported similar immune recovery between breast cancer survivors and the healthy group [63]. The effects of this acute exhaustive endurance exercise on immune response, such as the proportion of overall immune cells, T-cell subsets and pro-inflammatory cytokine levels were not different between the survivors and healthy subjects. However, the survivors showed significantly lower baseline levels of monocytes, T helper cells, and naive T-cell populations, whereas cytotoxic and memory T-cells are higher than the control group [63]. The reduction in baseline overall immune cells of the experimental subjects can be explained by the previous bone marrow suppressive treatments such as chemotherapy and radiation [63]. However, it can be hypothesized that the survivors of breast cancer after treatment and healthy subjects have the same recovery behavior and immune response after a single bout of endurance exercise [63]. Immune biomarkers in breast cancer can also be improved by resistance training. A 16 week-machine based weight training exercise in 20 breast cancer survivors resulted in lower levels of TNF-alpha, indicating that resistance training is likely to be advantageous in promoting an anti-inflammatory profile amongst breast cancer survivors [64]. The influence of various types of exercise training on biomarkers and physical changes are shown in Figure 1.

7. Conclusion and future prospects

Breast cancer affects women's well-being. The incidence rate tends to increase year by year, whereas mortality is decreasing worldwide. The possible risk factors of breast cancer are age, lifestyle, reproductive history, use of HRT and genetic mutations. Obese women are predisposed to developing breast cancer as a result of chronic pro-inflammatory milieu and hypoxic condition in breast tissue. Furthermore, weight gain after diagnosis has been shown to increase the mortality rate of breast cancer. Some biomarkers associated with adiposity and immune responses are used to correlate breast cancer prognosis. Biochemical substances related to fat metabolism such as insulin, adipokines and estrogen can precipitate mammary cell proliferation and cancer progression. Additionally, changes in immune functions, activation or suppression, are accepted predictors of breast cancer risks and breast cancer outcome. Exercise programs such as aerobic and weigh training have been reported to benefit breast cancer survival through adiposity and immune response changes. Several studies suggest that exercise can significantly reduce the mortality rate and improve the quality of life of breast cancer patients; as a consequence, exercise and physical activities have been recommended as an adjuvant therapy for breast cancer survivors.

Although numerous research studies support a significant role of exercise on immune function in cancer patients and some randomized clinical trials argue that an exercise program which reduces body fat can diminish breast cancer death rate, further mechanisms related to adiposity and immune responses to cancer outcomes still need to be determined. More specifically, studies of an appropriate exercise program for breast cancer survivors are needed with more clear comprehensive analysis of the adiposity and immune biomarker changes which are anticipated for positive health outcomes.

Conflict of interest

The authors have no conflict of interest to declare

Contributors

SP wrote the review article under the guidance of VA, LS, KT. All authors edited and reviewed the article.

Ethical approval

No ethics was required for this article

Funding

No funding was received specifically for this research article

Acknowledgements

SP would like to thank Assumption University, Bangkok Thailand for postgraduate scholarship. VA was supported by the Centre for Chronic Disease and all authors acknowledge the support of the College of Health and Biomedicine, Victoria University, Australia. VA was supported by the Victoria University start up funds.

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Table 1. The effects of different exercise regimes on breast cancer clinical outcomes

Types of exercise	Effects on clinical outcome	Reference
Regular exercise, occupational and leisure activities	- Reduces cancer-specific and all-cause mortality (Hazard ratio in survival rate)	[47]
Fast walking (3 hours/week) before and after diagnosis	- Exercise before diagnosis can lower all-cause mortality by 39 % - Exercise after diagnosis can reduce all-cause mortality by 46 % and reduce breast cancer-specific mortality by 39 %	[44]
Moderate to high intensity aerobic exercise (50-85% of maximal heart rate) for 3 time/week and range between 8-24 weeks	- Improves quality of life, ability to deal with daily tasks	[46]
Two aerobic and strength sessions per week; 60 minutes per session including 5 minutes-warm-up, 25 minutes-progressive aerobic exercise, 25-minutes weight training and 5 minutes-cool down, for 18 weeks (start early after diagnosis)	- Lowers physical and mental fatigue - Increases leg muscle strength	[1]
Self-directed exercise (during treatment period) : 12-week progressive aerobic exercise (low to moderate intensity walking; at least 20 minutes per day)	- Declines sleeping disturbance - Improves emotional status - Reduces symptoms of distress	[45]

Figure 1. The influence of exercise on immune biomarkers and physical change in breast cancer patients