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Physical Activity, Weight Control, and Biomarkers of Prognosis and Survival among Breast Cancer Survivors

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Abstract

Physical inactivity and obesity may increase risk of poor prognosis in breast cancer through effects on insulin or insulin-like growth factors or their binding proteins, insulin resistance, glucose metabolism, sex hormones, leptin and other adipokines, immunologic or inflammatory factors, oxidative stress, and Deoxyribonucleic acid (DNA) damage or repair capacity. The present review is based upon bibliographic searches in PubMed and relevant search terms. Articles published in English from January 1, 1980 through October 1, 2018 were identified using the following MeSH search terms and Boolean algebra commands: breast cancer survivors AND (insulin-like growth factor OR insulin resistance OR glucose metabolism OR sex hormones OR leptin OR adipokines OR immunologic OR inflammatory factors OR oxidative stress OR DNA repair capacity). After screening the abstracts or full texts of these articles and reviewing the references of previous review articles, a total of 66 studies met the eligibility criteria. Based upon published studies, it is difficult to determine the type or dose of exercise that affects inflammatory markers among breast cancer survivors. The optimal type of exercise, dose, and timing of physical activity needed to improve the inflammatory profile following a breast cancer diagnosis is unknown. Studies have used a range of physical activity types including aerobic, resistance training, yoga, and Tai Chi. A further issue is that existing studies of physical activity and biomarkers have included a range of disease stages. There is a need for a better understanding of the biological pathways through which physical activity and weight management increase survival in order to design targeted weight loss and exercise interventions for breast cancer survivors.

Keywords: Breast Cancer Survivors; C-reactive Protein; Estrogens; IGF-I; IL-6; Leptin; Obesity; Oxidative Stress; Physical Activity; Prognosis; TNF-α.

Introduction

Physical inactivity and excessive weight gain can occur following breast cancer treatment which increases risk of breast cancer recurrence, other chronic diseases, and all-cause and breast cancer-related mortality [1]. Physical inactivity increase risk of obesity and non-breast cancer mortality. Exercise can lower circulating levels of estrogen and potentially reduce tumor proliferation. Only about one-third of breast cancer survivors engage in the recommended level of physical activity [2]. In a cohort study of 533 women aged 65 years or older with breast cancer, Reeves, et al. [3] found that the risk of mortality was 1.4 times higher for a Body Mass Index (BMI) of 27.3 kg/m^2 (95% CI 1.03-2.01) and 2.4 times higher for a body mass index of 34.0 kg/m^2 (95% CI 1.07-5.45) compared with women with a BMI of 22.6 kg/m^2. Maliniak, et al. [4] studied 4,226 women aged 65 years or older with local or regional breast cancer. Pre- and post-diagnosis body BMI was associated with a higher risk of breast cancer-specific mortality (pre-diagnosis, Hazard Ratio [HR] 1.27, 95% confidence interval [CI] 1.14-1.41; post-diagnosis, HR 1.19, 95% CI 1.04-1.36). Neither pre- nor post-diagnosis physical activity was associated with breast cancer-specific mortality. BMI and physical activity were both significantly associated with all-cause mortality.

Although physical activity is an affordable and relatively convenient way to improve breast cancer outcomes, the biological pathways through which physical activity and weight management increase survival among breast cancer survivors are only partially understood. Results from animal studies and observational studies suggest that physical inactivity and obesity may increase risk of poor prognosis through effects on insulin or insulin-like growth factors or their binding proteins, insulin resistance, glucose metabolism, sex hormones, leptin and other adipokines, immunologic or inflammatory factors, oxidative stress, and DNA damage or repair capacity [5].

Methods

The present review is based upon bibliographic searches in PubMed and relevant search terms. Articles published in English from January 1, 1980 through October 1, 2018 were identified using the following MeSH search terms and Boolean algebra commands: breast cancer survivors AND (insulin-like growth factor OR insulin resistance OR glucose metabolism OR sex hormones OR leptin OR adipokines OR immunologic OR inflammatory factors OR oxidative stress OR DNA repair capacity). The searches were not limited to words appearing in the title of an article nor to studies in a particular country or geographic region of the world. The references of review articles were also reviewed. Information obtained from bibliographic searches (title and topic of article, information in abstract, study design, and key words) was used to determine whether to retain each article identified in this way. Only studies written in English that examined the impact of breast cancer survivorship care plans on health outcomes were eligible for inclusion. A total of 271 article citations were identified in PubMed. After screening the abstracts or full texts of these articles and reviewing the references of previous review articles, a total of 66 studies met the eligibility criteria.

Insulin-like Growth Factors

The biological mechanisms by which exercise reduces risk of breast cancer include alterations in plasma levels of insulin-like growth factor axis proteins. High insulin and Insulin-like Growth Factor-I (IGF-I) levels have been associated with an increased risk of breast cancer [1]. Higher insulin levels may contribute to increased tumor growth [6]. Elevated insulin levels, such as those associated with obesity, may increase the risk of breast cancer recurrence and death [7]. When IGF-I binds to its cognate receptor (IGF-1R), it triggers a signaling cascade that leads to proliferative and anti-apoptotic events. The IGF-I system is involved in breast cancer development, progression, and metastasis [8]. Prognostic studies have shown that expression of IGF-1R, the receptor for IGF-I, is predictive of improved survival and that its expression is related to hormone receptor status [9,10]. However, IGF-1R is a favorable prognostic indicator only in hormone receptor-positive breast cancers. IGF-1R positively reflects a well-differentiated tumor with low metastatic tendency [11]. Among women with triple-negative breast cancers, IGF-1R is a predictor of poorer survival [12].

High levels of IGF-I and insulin-like growth factor binding protein-3 (IGFBP-3) have been positively associated with breast cancer recurrence and death [13]. In a Randomized Controlled Trial (RCT) that enrolled 75 postmenopausal breast cancer survivors, Irwin, et al. [14] found that a moderate intensity, aerobic exercise intervention led to statistically significant decreases in IGF-I and IGFBP-3. Fairey, et al. [15] found that an exercise intervention led to no statistically significant changes in IGFBP-1 in a RCT involving 53 postmenopausal breast cancer survivors. However, statistically significant differences between groups were observed for changes in IGF-I, IGFBP-3, and IFG-I: IGFBP-3 molar ratio. In a RCT involving 85 breast cancer survivors, Schmitz, et al. [16] found that a weight training intervention led to statistically significant decreases in IGF-II. Levels of IGFBP-3 were statistically significantly decreased in the delayed treatment group. No significant changes in IGF-I, IGFBP-1, or IGFBP-2 were observed.

Sex Hormones

Estrogen exerts its action through binding to two different estrogen receptors (ERs), ER-alpha and/or ER-beta [17,18]. ER-alpha have more prognostic value in breast cancer than beta or the ratio alpha to beta. There is an age dependent difference in the distribution of breast cancer receptors [19]. Premenopausal cancer patients are more likely to be African American and have estrogen negative tumors with poorer prognosis. Postmenopausal breast cancer patients are more likely European Americans with generally estrogen positive tumors and have better prognosis. ER alpha Negative (ERN) rates increase during premenopausal period and then plateau in postmenopausal period. ER alpha Positive (ERP) tumors increase in a woman's lifetime with the peak in the seventies. Breast cancer risk increases with increasing concentrations of total estradiol, free estradiol, and estrogen that is not bound to sex hormone-binding globulin [20]. Estrogen can induce cell proliferation and stimulate tumor growth. Among postmenopausal women, physical activity decreases breast cancer risk by decreasing sex hormones [20]. In post-menopausal women, physical activity decreases estrogen produced by adipose tissue and increases sex hormone-binding globulin. The concentration of sex hormone-binding globulin is related to the bioavailability of sex steroids and risk of developing breast cancer [20].

Leptin and other Adipokines

Leptin and adiponectin may influence risk of breast cancer recurrence [21]. Leptin, which is produced mainly by adipocytes and circulates in the blood, may act as a mitogen on normal cells

and breast cancer cells [22]. Leptin secretion from adipose tissue is believed to promote breast cancer directly and independently and also through its effects on estrogen and insulin signaling pathways [23]. Leptin promotes breast cancer progression through the activation of mitogenic, anti-apoptotic, and metastatic pathways [24]. Although leptin activates some carcinogenic pathways, adiponectin appears to have a regulatory role in insulin resistance and to exert antineoplastic activities and interfere with leptin-induced processes [25].

In a RCT that enrolled 100 overweight or obese breast cancer survivors, Dieli-Conwright, et al. [26] found that leptin and adiponectin were statistically significantly improved after a moderate-to-vigorous aerobic and resistance exercise intervention compared with usual care. In a RCT involving 21 breast cancer survivors, Arikawa, et al. [27] found that a calorie reduction and exercise intervention led to lower plasma levels of leptin. In a RCT involving 66 triple-negative breast cancer survivors, Swisher, et al. [28] found that a moderate intensity exercise intervention had no effect on serum leptin or adiponectin. In the prospective study of 1,183 breast cancer survivors, Irwin, et al. [14] found lower leptin levels with higher levels of physical activity. Rogers et al. [29] found that a resistance training and aerobic exercise intervention had no effect on adiponectin in a RCT that enrolled 28 breast cancer survivors. In a RCT involving 101 breast cancer survivors, Ligibel, et al. [30] found no association between a cardiovascular and strength training exercise intervention and adiponectin.

Immunologic and Inflammatory Factors

Chronic inflammation has been associated with cancer in epidemiologic studies [31]. Systemic inflammation may be an important prognostic factor in breast cancer. One biological mechanism by which physical activity has positive health effects among breast cancer survivors may be its capacity to reduce low-grade inflammation [32]. Inflammation has been shown to be a tumor promotor [33]. Tissue necrosis factor-α (TNF- α) and other cytokines may play a role in tumor progression by aiding in the growth and survival of malignant cells, promoting angiogenesis and contributing to genomic instability [33,34]. Levels of TNF- α, interleukin-6 (IL-6), and C-reactive Protein (CRP) are elevated in patients with breast cancer [31]. Levels of IL-6 are associated with cancer stage, extent of metastasis, and breast cancer recurrence [35].

Recent meta-analyses found that exercise decreases serum concentrations of IL-2, IL-6, and TNF-α [32,36]. IL-2 is involved in the differentiation and proliferation of natural killer cells. Exercise may impact the proliferation of T and B cells and enhance natural killer cell activity [32]. IL-6 is an inflammation-responsive cytokine and TNF-α is a proinflammatory cytokine. IL-6 upregulates CRP in the liver. Physical activity may down regulate the expression of pro-inflammatory cytokines [33]. In a RCT that enrolled 66 triple-negative breast cancer survivors, Swisher, et al. [28] found that a moderate intensity exercise intervention had no effect on serum IL-6, TNF- α, or CRP. Hagstrom, et al. [37] found that a resistance training intervention led to lower natural killer cell expression of TNF-α in a RCT involving 39 breast cancer survivors. No significant changes between groups were observed in serum levels of IL-6, IL-10, TNF-α, or CRP. Kiecolt-Glaser, et al. [38] found that a yoga intervention led to decreases in IL-6 and IL-1β but not TNF-α in a RCT of 200 breast cancer survivors. In a RCT involving 75 breast cancer survivors, Jones, et al. [39] found that an aerobic exercise intervention had no effect on levels of IL-6, TNF- α, or CRP. However, in a secondary analysis, a statistically significant reduction in IL-6 was observed among women who achieved 80% of the intervention goal compared with those who did not. Friedenreich, et al. [40] found that a moderate to vigorous exercise intervention led to a significant decrease in CRP but no changes in IL-6 or TNF- α in a RCT that enrolled 320 breast cancer survivors. In a RCT involving 16 breast cancer survivors, Gomez, et al. [41] found that an aerobic and strength training exercise program was associated with levels of Cutaneous T cell-Attracting Chemokine (CTACK) but not IL-6 or other cytokines examined. Payne, et al. [42] found that a walking exercise intervention had no effect on IL-6 levels in a RCT involving 20 women with breast cancer. Hutnick, et al. [35] compared 28 breast cancer patients who participated in a resistance training and aerobic exercise with 21 patients who did not exercise. Plasma IL-6 was similar in both groups.

Metabolic syndrome, which is accompanied by a proinflammatory state, is associated with an increased risk of breast cancer recurrence among breast cancer survivors [43,44]. Metabolic syndrome, which increases risk of diabetes and cardiovascular disease, is a chronic complication of breast cancer treatment [45]. Some [26,46] but not all studies [47,48] have shown that physical activity attenuates metabolic syndrome in breast cancer survivors. Central obesity, a key component of metabolic syndrome, is associated with the secretion of pro-inflammatory cytokines including IL-6, TNF-α and CRP [49]. Visceral adipose tissue secretes a number of proteins including IL-6 and TNF-α which stimulate the liver to secrete CRP [50].

High levels of CRP, which is a marker of inflammation, are associated with poor breast cancer prognosis and increased mortality [13,44]. Obese breast cancer survivors have been found to be more likely to have metabolic dysfunction (insulin resistance and higher levels of glucose and insulin) and higher levels of CRP [51]. Physical activity may reduce CRP levels although, in a recent meta-analysis of the effect of exercise training on mediators of inflammation, no association was observed with CRP [32]. In a prospective study of 76 cancer survivors (39% breast cancer), Ricci, et al. [52] found that CRP levels were decreased by a combined aerobic and resistance training intervention. Levels

of CRP responded positively to the exercise intervention only among those participants with normal baseline levels of CRP. Arikawa, et al. [53] found that a calorie reduction and exercise intervention led to lower plasma levels of CRP in a RCT involving 21 breast cancer survivors. In a RCT that enrolled 31 breast cancer survivors, Bower, et al. [54] found that a yoga intervention led to a statistically significant effect of soluble tumor necrosis factor receptor type II, a marker of TNF activity. However, there were no statistically significant changes in IL-6 or CRP. In a RCT involving 26 breast cancer survivors, Rogers, et al. [29] found that a resistance training and aerobic exercise intervention led to non-significant changes in IL-6 and CRP in a RCT involving 28 breast cancer survivors. Guinan, et al. [51] found that an aerobic exercise intervention had no statistically significant effect on CRP levels. Campbell, et al. [55] found no statistically significant effect of a lifestyle intervention on CRP levels in a pre-, post-test trial involving 32 breast cancer survivors. Janelsins, et al. [56] examined the effects of a Tai Chi Chuan intervention involving 19 breast cancer survivors. The intervention had no effect on serum levels of IL-2 or IL-6. However, changes in fat-free mass were positively correlated with changes in IL-6 and negatively correlated with changes in serum IL-2. In a randomized controlled trial among 53 post-menopausal breast cancer survivors, Fairey, et al. [57,58] found that a ergometer exercise intervention had no effect on IL-1α, IL-6, or TNF-α. However, CRP decreased in the intervention group and increased in the control group.

Oxidative Stress, DNA Damage, and Repair Capacity

Oxidative stress, which may have a role in carcinogenesis, has also been examined in studies of breast cancer and physical activity [59]. We demonstrated a race dependent link between oxidative stress and mental stress induced blood pressure variability [60]. Physical activity increases the production of reactive oxygen species and, due to an adaptation that occurs over time, exercise increases antioxidant capabilities and counters oxidative insults [61]. High levels of reactive oxygen species can damage DNA and other cell components. Antioxidant mechanisms include those that are enzymatic (e.g., superoxide dismutase, glutathione peroxidase, myeloperoxidase, catalase) or non-enzymatic (e.g., vitamins and polyphenol molecules contained in the diet) [59]. The production of reactive oxygen species can lead to chromosomal instability, genomic mutations, and permanent DNA damage [62]. It has been hypothesized that oxidative damage markers can be positively impacted by exercise training through enhanced DNA damage repair mechanisms [63]. The balance of oxidative stress factors is mainly determined by enzymatic mechanisms although exogenous factors such as physical activity and dietary intake can also play an important role [64,65]. Exercise training increases oxidative damage repair enzyme capacity and reduces oxidative damage [65]. Antioxidants counteract increases in the production of free radicals and protect the body from oxidative damage by maintaining redox balance [59].

Conclusions

Physical activity may improve health outcomes among breast cancer survivors through effects on insulin or insulin-like growth factors or their binding proteins, insulin resistance, glucose metabolism, sex hormones, leptin and other adipokines, immunologic or inflammatory factors, oxidative stress, and DNA damage repair capacity [5]. Relatively few studies have examined the inflammatory response to exercise among breast cancer survivors. Based upon published studies, it is difficult to determine the type or dose of exercise that affects inflammatory markers. The optimal type of exercise, dose, and timing of physical activity needed to improve the inflammatory profile following a breast cancer diagnosis is unknown [33]. Studies have used a range of physical activity types including aerobic, resistance training, and Tai Chi. In addition, studies of physical activity and markers of inflammation and other biomarkers have rarely used accelerometers or other objective measures of physical activity [33]. A further issue is that existing studies of physical activity and biomarkers have included a range of disease stages. There is a need for a better understanding of the biological pathways through which physical activity and weight management increase survival in order to design targeted weight loss and exercise interventions for breast cancer survivors.

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