Review

Physical Exercise Positively Influences Breast Cancer Evolution

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Abstract

Breast cancer is one of the most commonly diagnosed types of cancer in women. Its pathogenesis involves genetic, hormonal, and environmental factors. A large body of evidence indicates that physical activity has positive effects on every aspect of breast cancer evolution, including prevention, medical treatment, and aftercare clinical settings. Thus, different types of exercise can influence the prevention and progression of the disease through several common mechanisms, such as reduction of insulin resistance and improvement of immunity and cardiovascular function. Furthermore, acute and chronic symptoms of breast cancer, such as cachexia, muscle mass loss, fatigue, cardiotoxicity, weight gain, hormone alterations, bone loss, and psychologic adverse effects, may all be favorably influenced by regular exercise. We review the relation of intensity and duration of exercise with potential pathophysiologic pathways, including obesity-related hormones and sex steroid hormone production, oxidative stress, epigenetic alterations such as DNA hypomethylation, and changes in telomere length, within the context of the beneficial effects of exercise. The potential role of exercise in reducing the intensity of the adverse effects that result from breast cancer and anticancer treatment is also discussed.

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Introduction

Breast cancer is one of the most commonly diagnosed types of cancer globally, accounting for one fourth of the cases of cancer among women and 11% overall, and constitutes the major cause of women's death by cancer.[1] According to epidemiologic research conducted by the World Health Organization,[2] cases of breast cancer have increased by more than 20% and mortality rates have risen by 14% between the years 2008 and 2012. The frequency of the disease is higher in developed countries, although its rates have also increased lately in developing countries.[2]

There is ample evidence that physical activity in the form of regular exercise has positive effects on breast cancer patients, not only during cancer treatment but also aftercare.[3-5] However, its direct contribution to cancer prevention has not yet been proved, despite the remarkable amount of research conducted in this field.[6] Nevertheless, the beneficial effects of exercise on the control of obesity have indirectly been associated with breast cancer prevention.[7,8]

This review analyses the relation between exercise and the prevention as well as treatment of breast cancer. This association involves type, intensity, and duration of exercise; menopause status; obesity; and potential pathophysiologic pathways, including those of obesity-related hormones, such as leptin and insulin-like growth factors (IGFs), as well as of estrogen production. Furthermore, hypothesized breast cancer–associated mechanisms involving oxidative stress, DNA hypomethylation, and changes in telomere length are also discussed within the context of the beneficial effects of exercise.

Pathogenesis of Breast Cancer

The pathogenesis of breast cancer involves genetic, hormonal, and environmental factors. Genetic predisposition seems to play an important role, and in the last few years, many genes connected with this type of cancer have been extensively investigated.[9-12] Carriers of modified alleles of these genes have higher risk of developing breast cancer. For example, mutations in the autosomal-dominant genes breast cancer 1 (*BRCA1*) and 2 (*BRCA2*) are responsible for 3% of breast cancer cases.[13,14]

In addition, there is a direct correlation between breast cancer development and hormone imbalance. High exposure to estrogens and the growth factors dependent on them can influence tumor

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growth and progression. Moreover, environmental factors such as healthy dietary habits, lactation, regular exercise, and limited alcohol consumption decrease the risk of both pre- and postmenopausal breast cancer.[14]

Exercise might not have any effect on the genetic background of the disease; however, it can sufficiently influence both the hormonal and the environmental elements of the disease. Different types of exercise, such as aerobic and resistance training, depending on their duration and intensity, may affect in various ways both the prevention and the progression of the disease.[4,5,15]

Pathophysiologic Mechanisms, Risk Factors, and Exercise

Exercise may decrease the risk of breast cancer occurrence through various pathophysiologic pathways. Some of those pathways have been established, while there are indications of the preventive effect of others (Figure 1).

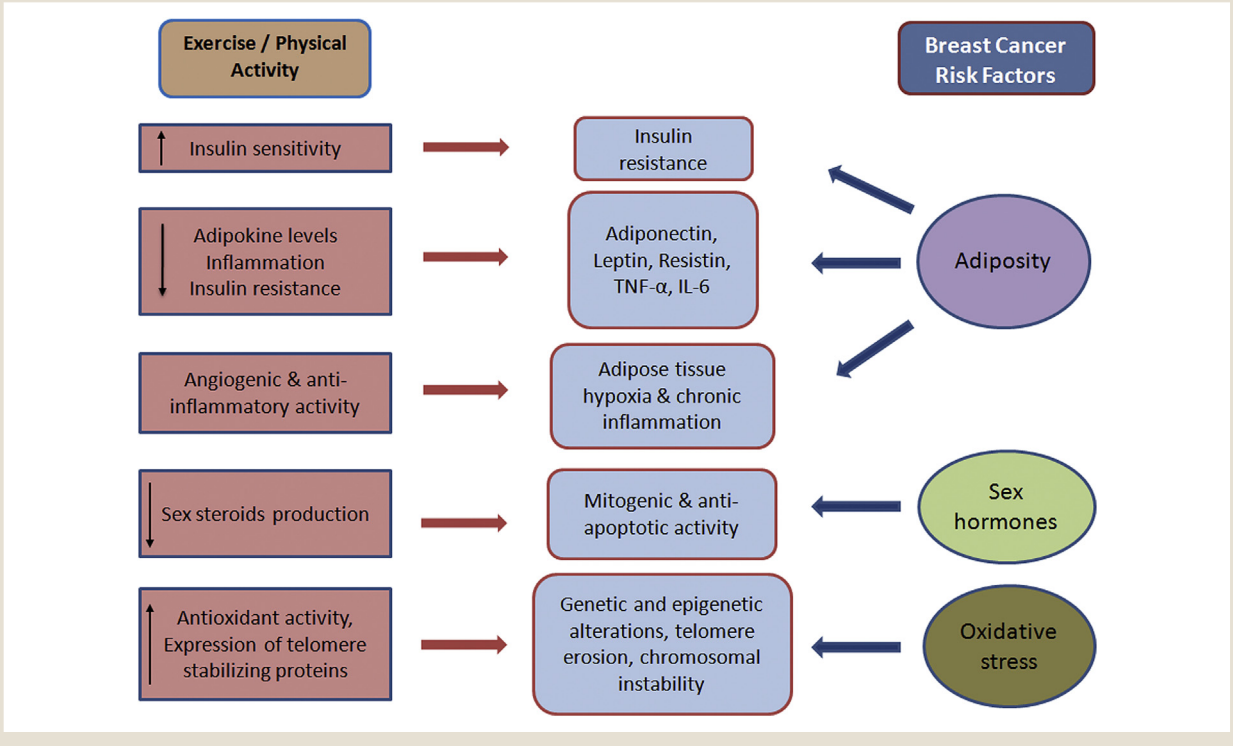
Adiposity. According to epidemiologic studies, approximately 15% to 20% of all cancer deaths can be attributed to obesity.[16] Specifically, overweight and obesity, as demonstrated by a high body mass index (BMI), have been linked to increased risk of cancer in general and particularly of breast neoplasms. Other indicators of body fat distribution, such as waist circumference and waist-to-hip ratio, have been also connected to breast cancer risk.[17] Particularly in postmenopausal women, there is a direct correlation between excess weight and breast cancer occurrence, as opposed to premenopausal women, where no direct association has been found.[18] Interestingly, weight gain during adulthood is linked with higher risk of postmenopausal breast cancer among women who do not receive menopausal hormone therapy.[19]

In contrast with risk factors such as genetic background, menopausal status, and age, adiposity is a reversible and preventable risk factor.[20] The main role of adipose tissue is the storage of excess calories as converted triacylglycerols and the secretion of free fatty acids (FFA); it also constitutes an important endocrine and immune organ.[21,22] Nevertheless, adiposity can be associated with cancer development and progression through 3 different mechanisms, discussed next: insulin resistance, adipokines and chronic inflammation, and adipose tissue hypoxia (Figure 1).

Insulin resistance

Insulin mainly regulates the metabolism of carbohydrates, lipids, and proteins; however, it also acts as a growth factor.[23] Thus, similar to the mitogenic and antiapoptotic actions that circulating IGF-1 exerts in breast cancer cells,[24-26] insulin stimulates the growth of breast cancer cells through binding with insulin and IGF-1 receptors.[27] In addition, insulin is associated with estrogen-induced mitosis by raising the bioavailability of sex hormones through a reduction in sex hormone binding globulin (SHBG), while it also promotes angiogenesis through the expression and secretion of vascular endothelial growth factor in breast cancer cells.[28] Moreover, insulin resistance and the consequent hyperinsulinemia are connected with other breast cancer risk factors, such

Figure 1 Risk Factors and Pathophysiologic Mechanisms of Breast Cancer, and Role of Physical Activity in Their Modulation. Blue Arrows Indicate Promoting Effect; Red Arrows, Counteracting Effect



Abbreviations: IL-6 = interleukin 6; TNF-α = tumor necrosis factor alpha.

as obesity, adipokines, and proinflammatory mediators. Physical activity, including both aerobic and resistance exercise, has protective effects on cancer risk because it improves insulin sensitivity, reduces circulating insulin levels, increases glucose intake by skeletal muscle, and lowers fatty acid synthesis.[29]

Adipokines and chronic inflammation

Adipokines are bioactive polypeptides secreted by adipocytes, fibroblasts, and local macrophages that may influence breast cancer development directly, through their mitogenic, antiapoptotic, and invasive- and metastatic-inducing action, and indirectly, by promoting inflammation, insulin resistance, and estrogen bioactivity. The most influential adipokines for breast cancer include leptin, adiponectin, tumor necrosis factor alpha (TNF-α), and interleukin (IL) 6 (Figure 1).[30]

Chronic, low-grade inflammation caused by obesity leads to adipose tissue dysfunction and remodeling, and creates a microenvironment favorable to neoplasm development (Figure 1). The presumed mechanisms involved in the induction of inflammation include lipotoxicity, hypoxia of the hypertrophic adipocytes, higher lipid concentration, which causes endoplasmic reticulum stress, and activation of Toll-like receptor by FFAs.[31] Furthermore, increased adiposity and the consequent immune response result in adipocyte hypertrophy and dysfunction, immune cell accumulation, angiogenesis, and fibrosis, as well as altered pattern of adipokine and chemokine release.[31]

Macrophage recruitment to the adipose tissue has been proved to promote carcinogenesis through enhanced levels of chemotactic and inflammatory signals, which are found to be dysregulated in breast cancer.[20] Monocytes are attracted by secreted chemokines,[32] and their production is stimulated by increased FFAs and adipokines that stimulate inflammation, such as TNF-α.[31,33]

Adipose tissue macrophages and tumor-associated macrophages are polarized in 2 different cell populations, M1 (proinflammatory) and M2 (anti-inflammatory), whose activation leads to different biochemical pathways.[31,33] M1 cells manifest proinflammatory actions by cytokine secretion (TNF-α, monocyte chemotactic protein [MCP] 1, IL-6, and IL-1β) and are associated with the development of insulin resistance and tumorigenesis.[31,33,34] M2 cells protect against inflammation and insulin resistance through the production of IL-10, IL-1Ra, and arginase. During weight gain and tumorigenesis, a switch from M2 to M1 cells has been observed, promoting local and systemic inflammatory response and insulin resistance.

It should be noted, however, that M2 macrophages express anti-inflammatory cytokines that provide an immunosuppressive microenvironment that favors tumor growth, while M1 macrophages may also secrete cytokines that exert cytotoxic activity on tumor cells and promote antitumor immune responses.[35] Thus, the M2 to M1 transition during weight gain could compromise the outcomes among cancer patients. Overall, the role of tumor-associated macrophages in breast cancer progression needs further characterization.[35] There are various mechanisms by which exercise may reduce chronic inflammation and adipokine production. Exercise acts simultaneously in different tissues with multiple effects. These include a reduction in leukocyte and cytokine production, as well as a systematic effect on endothelial cells to lower their potential for leukocyte adhesion and cytokine production. Exercise may also result in higher myokine secretion from muscle tissue, which leads to anti-inflammatory actions and may improve adipose tissue hypoxia.[36] Moreover, exercise shifts the balance of adipokines by favoring the secretion of anti-inflammatory and antimitotic mediators, such as adiponectin, while simultaneously reducing the production of antiapoptotic and proinflammatory adipokines, such as leptin and TNF-α. The combined result of the abovementioned mechanisms leads to a microenvironment less favorable to the development of neoplastic tissue. More specifically, adipokines manifest various responses to physical activity; adiponectin levels may be increased during exercise of average intensity, especially in overweight individuals. In addition, leptin levels might be lowered through strenuous long-term exercise (more than 3 months); however, in short-term training programs, no significant changes are observed.[37] Moreover, exercise reduces TNF-α levels and alters the responsiveness to this cytokine through multiple pathways.[37] Moderate exercise can also induce a prolonged increase in IL-6 secretion from the adipose tissue, which stimulates lipolysis and FFA mobilization through both autocrine and paracrine pathways.[38]

Adipose tissue hypoxia

The increase in adipose tissue mass and the hypertrophy of adipocytes lead to the development of tissue hypoxia. The subsequent diminishment in oxygen concentration in the adipose tissue activates inflammatory and angiogenic pathways, recruits macrophages and alters the adipokine secretion pattern.[39] Hypoxia-inducible factor 1 (HIF-1), a transcription factor accumulating in hypoxia, promotes the mRNA expression of multiple genes that stimulate inflammation, angiogenesis, and erythropoiesis.[40] Moreover, it induces alterations in cellular metabolism, such as a shift from oxidative phosphorylation to glycolysis. The abovementioned mechanisms create a hypoxic environment favorable to the development of breast neoplasm. Exercise may reverse those effects through the stimulation of angiogenesis in adipose tissue and thus an increase in tissue blood flow (Figure 1).[36]

Sex Hormones

Sex hormones act as strong mitogens and obstruct apoptosis in many tissues, including the breast, which is one of their main targets. Furthermore, metabolic products of the estrogen oxidation can manifest mutagenic and genotoxic effects.[41]

The main source of estrogens in postmenopausal women is the adipose tissue, which is the main site of action for the enzymes (mainly aromatase and 17β-hydroxysteroid dehydrogenases) that convert androgens to estrogens. Thus, overweight postmenopausal women present higher levels of sex hormones and lower levels of sex hormone-binding globulin (SHBG) in their blood serum compared to normal-weight women.[42]

There is strong evidence that exercise decreases the secretion of endogenous estrogens and androgens and that this is achieved through the limitation of body fat (Figure 1).[43] In particular, in a randomized controlled trial examining the relation between exercise and sex hormone levels, postmenopausal women followed three 12-month diet and exercise interventions, and their estrogen, androgen, and SHBG levels were compared to those of control subjects. The results of the study showed that estrone and estradiol levels decreased significantly with a combined diet and exercise intervention, whereas in the case of exercise alone the decrease was less pronounced. Total testosterone

and androstenedione levels showed no notable changes, while SHBG levels increased considerably in the case of the combined weight loss and exercise intervention.[43]

As far as premenopausal women are concerned, the mechanisms are less well defined and the research data ambiguous. Specifically, a group of premenopausal women (31.5 years old on average) underwent a 4-month calorie restriction and moderate exercise program in order to determine the relation of these factors to urinary estrogen metabolites.[44] It was found that although diet and exercise may lead to lower risk of breast cancer in the long term, there is no direct association between these factors and estrogen levels.[44] Nevertheless, intense exercise has been linked not only to menstrual dysfunctions, such as delayed menarche, amenorrhea, or oligomenorrhea, but also to less acute changes, such as anovulation. These disruptions result in lower estrogen production.[45]

Androgens interact with breast cells both directly, via their receptors that enhance cell proliferation, and indirectly, via their conversion to estrogens.[46] Specifically, before but also after menopause, androstenedione is converted to testosterone and dihydrotestosterone in many tissues, such as ovaries, adipose, and breast. Particularly testosterone constitutes the most active androgen form, while its bioavailability can be decreased by physical exercise through the diminishment of adipose tissue or the increase of SHBG levels.[46]

Oxidative Stress, Epigenetic Alterations, and Telomere Length

One of the hypothesized mechanisms involved in the pathogenesis of breast cancer is oxidative stress, caused by an imbalance between the production of free radicals and their neutralization by antioxidants (Figure 1).[47,48] Free radicals include reactive oxygen and nitrogen species, which possess one or more unpaired electrons and therefore demonstrate a very unstable and reactive nature, leading to cellular, functional, and structural decline through their damaging effect on lipids, carbohydrates, proteins, and nucleic acids.[48]

The main carcinogenetic activity of oxidative stress can be attributed to the genetic alterations it exerts. In particular, free radicals may react with pyrimidines, purines, and chromatin proteins, thus modifying the pattern of gene expression and reinforcing the mutation potential. DNA damage, combined with the impairment of repair mechanisms, might lead to the activation of oncogenes and the suppression of tumor suppressor genes, causing an oncogenic phenotype.[47] Furthermore, oxidative stress is responsible for epigenetic alterations, such as global DNA hypomethylation, which promotes genomic instability and protooncogene activation, as well as regional hypermethylation of the promoter of tumor suppressor genes, which results in gene silencing (Figure 1).[47]

Depending on the type, duration, and intensity of exercise, multiple influences on breast cancer risk can occur.[49] Specifically, regular exercise of moderate intensity acts preventively for carcinogenesis, as it benefits antioxidant and oxidative damage, repairing enzymes and enhances inflammation-related gene expression. However, exhaustive exercise on unprepared tissues can cause a significant increase in reactive oxygen species production due to the raise in oxygen and adenosine triphosphate consumption, resulting in an altered cellular redox state.[49]

Moreover, oxidative stress can erode telomeres, therefore causing chromosomal instability. Telomeres constitute protective chromosomal caps, the length of which is maintained via the action of telomerase; telomere dysfunction and telomerase reactivation is associated with a higher risk of cancer.[50] Excess weight has also been related to shortened telomeres through obesity-induced chronic inflammation and oxidative stress. Exercise can positively influence telomere maintenance by promoting the expression of telomere-stabilizing proteins and by protecting against oxidative stress (Figure 1).[51]

Population Groups

Depending on women's specific characteristics, multiple variables are associated with breast cancer risk. These include menopausal status, age of menarche, race, and family history of breast cancer.

In particular, early menarche has been associated with increased breast cancer risk as a result of the earlier onset of menstrual cycles and therefore longer estrogen secretion and circulation, which promote cell division. According to Clavel-Chapelon and Gerber,[52] for every additional year in the age of menarche, there is a decrease in breast cancer risk by approximately 9% in the cases of premenopausal diagnosis and by 4% when breast cancer is diagnosed later. An early menarche combined with a late menopause result in longer exposure to estrogens, thus increasing the risk of breast cancer occurrence.[52]

Strenuous exercise can delay menarche by influencing the hypothalamic–pituitary–adrenal axis, resulting in disturbances in hypothalamic function and gonadotropin-releasing hormone release. Inhibition of gonadotropin-releasing hormone secretion leads mainly to a limited production of luteinizing hormone and secondarily of follicle-stimulating hormone, and therefore to a lower estradiol synthesis and ovarian stimulation. Interestingly, this effect is more pronounced when exercise is combined with restriction of caloric intake.[53] Furthermore, studies have provided evidence for the beneficial role of exercise in reducing breast cancer risk, both in pre- and postmenopausal women, by 27% and 31%, respectively.[18]

Breast cancer occurrence may also be related to the age of first full-term pregnancy as well as further pregnancies; there is a significant increase of breast cancer risk associated with older age at first full-term pregnancy and a considerable risk reduction with every full-term pregnancy.[52] In addition, lactation can act protectively against breast oncogenesis by inducing the differentiation of breast tissue and therefore rendering it less susceptible to carcinogens. Moreover, breastfeeding suspends ovulation, contributing to the reduction of ovulatory hormones. The positive effect of breastfeeding is also proportionally increased with its duration, having significant results when lasting 12 months or longer.[54]

Breast cancer incidence rates also differ depending on race, according to epidemiologic data from the World Health Organization.[55] Higher rates are demonstrated in more developed regions, with an occurrence of more than 90 per 100,000 in Western Europe and Northern America; the lowest rates are observed in Eastern Asia and Middle Africa, with fewer than 30 per 100,000.[55] Physical exercise helps reduce breast cancer risk, with stronger effects on nonwhite women, with 41% relative decrease among black and Asian, 38% among Indian, and 28% among Hispanic

women. Interestingly, among white women, the risk reduction appears significantly lower (20%).[18]

Another factor involved in breast cancer risk is genetic predisposition. *BRCA1* and *BRCA2* are the main genes the mutation of which is most commonly associated with breast tumorigenesis.[13,14] Other genes with a significant role include the following: tumor protein p53 (TP53), a tumor suppressor gene that normally induces apoptosis in cases of cellular dysfunction and is found mutated in most neoplasm cases; phosphatase and tensin homolog (PTEN), a cell growth regulator and tumor suppressor; and CHEK2 checkpoint kinase 2 (CHEK2), a serine–threonine kinase that regulates the expression of DNA repair proteins in response to genetic damage. Significant beneficial effects of physical activity in women without a family history of breast cancer are manifested by a 21% risk reduction; however, no considerable effects (less than 1%) were observed among women with a family history.[18]

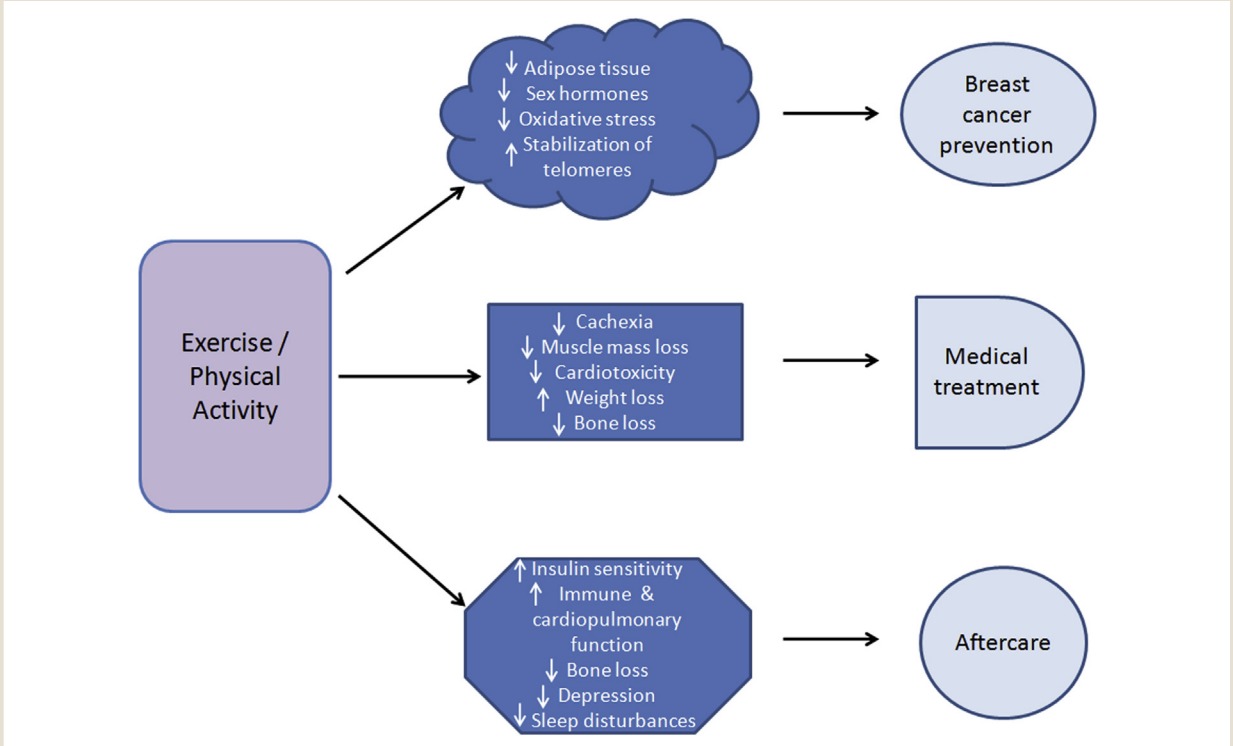
Role of Exercise in Breast Cancer Prevention

A reverse relation between exercise and breast cancer has been observed in multiple studies, with a significant risk reduction for postmenopausal cancer ranging from 20% to 80% and a weaker effect for premenopausal women. The combined impact of exercise on both pre- and postmenopausal breast cancer was found to decrease the risk by approximately 15% to 20%.[56] Moreover, exercise during childhood and adolescence may contribute to breast cancer prevention through a reduction in fat stores and exposure to sex hormones. Habitual exercise patterns in early life are usually sustained during adulthood, therefore maximizing their beneficial effects on adult health (Figure 2).[57]

In particular, the extent of the exercise-induced reduction of breast cancer risk varies depending on the type and the specific characteristics of exercise. The different categories of physical activity include recreational (performed at leisure time for enjoyment), occupational (at work), household (at home), and transport (done to commute) activities. Physical activity and exercise can also be categorized into aerobic/endurance (eg, brisk walking, jogging, dancing), strength/resistance training (eg, weight lifting), and balance and flexibility exercises. The greatest risk reductions were found in cases of recreational and household activities (21%), closely followed by occupational activities (18%), while active transportation physical activity, such as walking and cycling, were found to provide more modest results (13%).[58]

Moreover, several studies have suggested a dose–response relationship between exercise and breast cancer risk, with a greater benefit being observed with a higher frequency and duration of activity. Thus, while 2 to 3 hours of weekly exercise was associated with an average risk reduction of 7%, 6.5 hours per week raised that percentage to almost 30%.[59] Moreover, depending on its intensity, exercise can be stratified as light, moderate, or vigorous. Women participating in vigorous physical activities exhibited slightly greater risk reductions (26%) compared to those taking part in moderate-intensity exercises (22%).[60] Overall, a large body of evidence indicates that the strongest association between exercise and cancer risk reduction is expected for moderate to vigorous recreational activity, regularly maintained over lifetime (Figure 2).

Figure 2 Beneficial Effects of Physical Activity on Various Aspects of Breast Cancer



Role of Exercise in Breast Cancer During Medical Treatment

The various benefits of exercise affect not only the preventative goals for breast cancer but also the stages after its diagnosis and during its treatment. The physical and psychologic adverse effects of the medical treatment for breast tumors can be moderated by different degrees by multiple types of exercise (Figure 2).

Depending on the stage of the diagnosed breast tumor, different curative methods are selected and applied. Surgery is preferred as treatment in most cases, and according to the tumor size and lymph node infiltration, either lymphectomy or mastectomy may be chosen.[61] Radiotherapy is a regular choice after lymphectomy, and in some specific cases after mastectomy (breast tumors stages II and III), to destroy any remaining cancer cells. Chemotherapy is used both before surgery to shrink the tumor and after surgery to limit the risk of cancer recurrence. A more contemporary, targeted type of chemotherapy is biologic therapy, which is provided specifically to women with human epidermal growth factor receptor 2 (HER-2)-positive cancer. Endocrine therapy is another alternative, mostly used after surgery in women with hormone receptor−positive cancer, limiting the enhancing effect of estrogens on the tumor.[61] Regardless of the therapeutic effects of the abovementioned treatment methods, there are significant adverse effects concerning both physical and psychological health factors of breast cancer patients. Acute symptoms include loss of appetite accompanied by nausea, vomiting, and diarrhea; bleeding; lowered resistance to infection; hair loss; muscle weakness; and fatigue. Chronic adverse effects are cardiovascular toxicity, ovarian dysfunction and premature menopause, weight gain, and bone loss.[62]

Next we describe the potential of exercise to reduce the intensity of the adverse effects that result from both the cancer itself and the anticancer treatment, thus improving the patients' physical performance and quality of life (Figure 2).

Cachexia

Cachexia is a chronic inflammatory condition emanating from an increased cytokine secretion from the tumor and the host tissues and results from an imbalance between protein synthesis and protein catabolism. It constitutes not only a paraneoplastic syndrome but also an adverse effect of breast cancer treatment, reducing the quality of life as well as the response to anticancer treatment.[63] It includes a variety of pathologic manifestations such as anorexia, muscle weakness, adipose tissue depletion, and weight loss.

As already mentioned, exercise helps counter chronic inflammation and cytokine production, lowering the levels of proinflammatory cytokines while also enhancing the secretion of anti-inflammatory mediators.[64] The latter include the myokines—that is, muscle-derived cytokines with endocrine actions, which exert systemic anti-inflammatory effects and cause local increase of muscle glucose uptake.[65]

Moreover, the atrophy of muscle tissue during breast cancer therapy may lead to an increased toxicity of the adverse effects and a decreased response to treatment. In addition, chemotherapy may be responsible for inducing peripheral neuropathy, cardiac and skeletal myotoxicity, and neurotoxicity. The metabolic status of these patients consists of a functional decline stemming from reduced muscle contractility.[66] Muscle atrophy can also occur during breast cancer radiotherapy, which affects the resident myogenic stem cells (satellite cells) by inducing cell cycle cessation at the G1/S and G2/M checkpoints and apoptosis.[67]

Aerobic and resistance exercise training can contribute not only to the prevention but also to the treatment of cachexia. More specifically, aerobic exercise positively affects skeletal muscle, reversing the effects of chronic cachexia and enhancing muscle function by inducing higher enzyme activity, myofibrillar protein synthesis, and mitochondrial biogenesis.[68] Furthermore, both aerobic and resistance exercise can inhibit the cancer treatment−induced loss of muscle mass and subsequent weakness.[67,69] This can be achieved through the activation of muscle satellite cells, which respond to exercise by reentering the cell cycle and multiplying. These cells can then contribute their nuclear material into the fiber to facilitate muscle regeneration and hypertrophy.[70] This effect is more pronounced in the case of strenuous resistance exercise training, which evokes a more significant muscle repair and regeneration response, leading to increased body strength and flexibility.[67] It is noted, however, that cancer therapy damages rapidly dividing cells and thus has the potential to target the activated satellite cells, so losses in this progenitor population via resistance exercise and cancer therapy may impair the maintenance of muscle mass during aging. Therefore, more information about cancer treatment effects on the activated satellite cells is needed before recommending resistance training during breast cancer treatment.[67] On the other hand, exercise can also help counter oxidative stress caused by radiotherapy and chemotherapy through its antioxidant effects and the activation of oxidative damage repairing enzymes.

Cancer-Related Fatigue (CRF)

Muscle mass loss is a factor associated with CRF. CRF is a condition of persistent weariness caused either by the tumor or by the cancer treatment. It is associated with abnormal metabolic changes, depletion of metabolic substrates, chronic stress response, hormone alterations, and skeletal muscle neurophysiologic modifications.[71] Apart from muscle atrophy, other mediators of CRF include proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, and interferon gamma, which lead to insulin resistance, higher cortisol and glucagon levels, protein and fat catabolism, weight loss, and anorexia.[71]

Several studies have been conducted in order to investigate the effects of exercise on CRF. It is well established that exercise is a low-cost, safe, and effective intervention for the improvement of fatigue and quality of life in patients receiving chemotherapy or radiotherapy for breast cancer. Multiple clinical trials have verified the beneficial outcome of exercise programs, emphasizing the importance of professional supervision at health centers to ensure patient safety and adhesion to the program.[72-74] A home-based exercise program, specifically tailored for each patient, is also recommended, which can lead to less physical and emotional distress as well as higher functional ability.[75] More specifically, an exercise interval of minimum 90 minutes per week has been suggested, divided into 3 or more moderate walking sessions and applied during a 6-week radiotherapy regimen or during a period of 4 to 6 months of adjuvant chemotherapy. Women who complied with this program reported decreased fatigue and higher functional capacity compared to those who were less active during the breast cancer treatment.[76]

Cardiotoxicity

Cardiotoxicity is also a chronic adverse effect induced by standard breast cancer treatment such as chemotherapy, characterized by a dose-dependent decrease in left ventricular function and an increase in the incidence of symptomatic heart failure.[77] Daily exercise has various established benefits on the cardiovascular system, as it controls body weight, improves blood circulation, and diminishes cholesterol levels and hypertension, and therefore results in the reduction of the risk of heart disease. In particular, not only acute but also chronic exercise is cardioprotective through its stimulating effect on antioxidant production and activity, including the main antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase.[78,79]

Weight Gain

Weight gain during cancer treatment constitutes a matter of concern because of its negative effect on self-esteem as well as on quality of life. Several mechanisms have been proposed for this chronic adverse effect, including mainly chemotherapy and radiotherapy, hormone imbalances, metabolic changes, and menopausal status.[80-82]

Weight gain is caused by an imbalance between caloric intake and expenditure due to metabolic alterations. These alterations can be induced by cancer treatment–related hormone changes and menopause; body weight and body composition may change with menopause, as the reduction of estrogen levels leads to alterations in fat distribution, which shifts from the hips to the waist. Great increases in fat mass are associated with premenopausal women who experienced chemotherapy-induced amenorrhea and therefore became menopausal. In addition, insulin resistance constitutes not only a treatment adverse effect that can lead to weight gain but also a result of increased adipose tissue. The increase in abdominal fat is associated with various negative effects, such as augmentation of circulating cortisol and adipokine levels, resulting in an abnormal metabolic profile.[82] Furthermore, obesity may lead to more serious conditions, including diabetes, metabolic syndrome, and cardiovascular dysfunction, as well as poorer cancer prognosis and surgical outcome.[83]

Another potential prognostic factor for weight gain is the pretreatment BMI; women closer to the ideal BMI are more likely to gain weight during breast cancer treatment compared to women with higher BMI (> 30 kg/m^2).[84-86] Moreover, psychologic factors are also involved in the weight gain through their influence on eating habits and the decrease of physical activity levels. Cancer treatment may promote a more sedentary lifestyle as a result of physical and psychologic fatigue, finally resulting in inactivity.[80]

Because the lack of exercise is an important factor related to weight gain, it has been suggested that cancer patients should be strongly encouraged to exercise in order to promote weight loss, attain and maintain a healthy weight, reduce inflammation, and improve their quality or life.[5,78]

Bone Loss

Bone loss constitutes another chronic adverse effect of breast cancer treatment, resulting from chemotherapy, radiotherapy, and hormone therapy, which all cause premature menopause, estrogen reduction, and bone mineral density depletion.[87]

In particular, chemotherapy-induced ovary failure is a clinical syndrome that includes a variety of symptoms such as menstrual or menopausal manifestations and bone loss.[88,89] The onset of bone loss appears as early as 6 months after the initiation of chemotherapy, and the mechanism of its pathogenesis involves the abrupt decrease of estrogen levels. Estrogens play a significant role in maintaining bone mass through their stimulating effects on osteoprotegerin production. Bones undergo a constant remodeling process through an established balance between osteoclast and osteoblast function. Osteoblasts enable bone construction while osteoclasts activate bone resorption, following an interaction between receptor activator of nuclear factor κB and its ligand (RANK-RANKL). Osteoblasts secrete osteoprotegerin, which inhibits the RANK-RANKL interaction and therefore the process of osteolysis.[89,90] Hormone therapy for breast cancer, such as aromatase inhibitors, have depleting effects on estrogen levels associated with accelerated bone resorption. Hence, both chemotherapy and hormone treatment lead to increased incidence of bone fractures and disfigurement, and thus to loss of self-esteem.[91]

Pathologic and Psychologic Disorders

Cancer treatment may lead to several psychologic disorders, such as depression, anxiety, and low self-esteem. Depression is a common condition among breast cancer survivors, and it is related to factors concerning both the patient (eg, loneliness, emotional support) and the type of treatment received, as well as to disease recurrence. The incidence of depression symptoms after breast cancer diagnosis and during the treatment ranges from 20% and 30%.[92] Depression has been associated with alterations in body composition and its image as it is perceived by the patient. Physical activity and exercise has been found to protect breast cancer survivors against depression via their functional improvement and muscular strengthening.[93]

Moreover, both hormone therapy and chemotherapy influence the hypothalamic–pituitary–adrenal axis, leading to an imbalance of circulating cortisol, serotonin, IL-6, and bilirubin levels. It has been suggested that serotonin levels influence sleep patterns as well as the quality and quantity of sleep, and there is evidence suggesting a possible association between depression, fatigue, and sleep disturbances induced by hypothalamic–pituitary–adrenal axis dysfunction.[94] Sleep disturbances, in terms of duration, time of onset, efficiency, early- or midcycle awakening, quality, and latency, are also common occurrences (20%-70%) in breast cancer survivors.[95] In particular, insomnia is more frequent among breast cancer survivors than among healthy women, and its pharmacologic treatment has been found insufficient.[96] The significant decrease in serotonin levels has been proposed as a potential mechanism through which exercise can exert its positive effects on those symptoms. Exercise has been proven beneficial for the control of sleep duration disturbances through its anti-inflammatory effects. More specifically, IL-10 and TNF-α are involved in most of the sleep outcomes, and exercise plays a major role in balancing the circulating levels of these cytokines.[97] Furthermore, it has been found that both aerobic and resistance exercise training can preserve fitness and muscular strength and lead to the improvement of the abovementioned psychologic disorders.[98]

To recapitulate the role of exercise in breast cancer during medical treatment, there is ample evidence that physical exercise can

not only prevent the occurrence of breast cancer treatment adverse effects but also reduce their importance. More specifically, both acute and chronic symptoms of breast cancer adverse effects, such as cachexia, muscle mass loss, fatigue, cardiotoxicity, weight gain, and bone loss, as well as psychologic adverse effects, may all be favorably affected by regular exercise and physical activity during both medical treatment aftercare (Figure 2).

Physical Activity in Breast Cancer Patients During Aftercare

Breast cancer has an excellent prognosis, with an estimated 5-year survival rate, verging on 90% when diagnosed in the early stages. Nevertheless, breast cancer survivors may face various late effects, depending on the type of treatment they received and on their individual characteristics. Those late effects include depression, anxiety, physical and sexual dysfunction, sleep disturbances, weight gain, and chronic fatigue, which collectively worsen the patients' quality of life.[99]

There are a great number of studies investigating evidence-based rehabilitation interventions for cancer survivors, and particularly how to deal with the aftereffects of breast cancer treatment during the rehabilitation process.[100-102] It has been suggested that those patients should be encouraged to exercise regularly after the treatment at a moderate level of intensity. Physical activity may include aerobic exercise (eg, walking or cycling), resistance exercise, or a combination. The training program should be adapted to each individual, depending on the patient's age and level of physical fitness.[100,101] Exercise provides established physical and psychologic benefits in breast cancer survivors.[3-5,43,103,104] In particular, aerobic exercise has beneficial effects on cardiopulmonary and immune function, insulin sensitivity, and physical performance, while resistance exercise training has also been shown to lead to physical and psychologic improvements via its positive influence on mediators of chronic diseases (Figure 2).[105]

A set of guidelines has been established to prevent and ameliorate the treatment-induced physical impairments of the patients.[102] Impairments of arm strength and range of motion can be countered with physiotherapy, beginning with gentle exercises and progressing to active stretching and later to resistance exercise.[102] Thus, a study examining the impact of weight training on breast cancer survivors suggested that this type of exercise twice a week can lead to alterations in body strength and body composition, particularly an increase in lean muscle mass, which significantly improved patients' quality of life.[15]

Lymphedema can be reduced mainly by decongestive therapy, while evidence exist that manual lymph drainage, compression, and massage therapy might also be effective. Exercise could also contribute to relief from lymphedema through its weight-reducing effects because a BMI of > 30 kg/m^2 is a potential risk factor for lymphedema. Furthermore, physical activity and exercise have been suggested in conditions of moderate pain as well as in chemotherapy-induced peripheral neuropathy in the form of physical or occupational therapy. As far as treatment-related cardiotoxicity is concerned, moderate exercise should be combined with a healthy diet and smoking cessation in order to preserve the myocardium.[102]

In addition, breast cancer survivors are often confronted with loss of bone mass, which might lead to osteoporosis and bone fractures. These conditions are caused by cancer treatment and its adverse effects, mainly chemotherapy-induced ovary failure, estrogen depletion, and fat gain.[106] Exercise has been shown to have significantly positive effects on the preservation of bone mineral density at the spine and hip of postmenopausal women.[107] Overall, it appears that most breast cancer survivors can safely participate in regular moderate-intensity exercise and improve various functional, physiologic, and psychologic parameters (Figure 2).[105]

Conclusions

Exercise has been proven to positively affect every aspect of breast cancer, including its prevention, medical treatment, and aftercare. Several common mechanisms are responsible, such as depletion of adipose tissue, bone and muscle mass preservation, reduction of insulin resistance, and improvement of immune and cardiovascular function. Thus, exercise may reduce the risk for breast cancer occurrence, ameliorate the patient's physical and psychologic condition during medical treatment, and improve quality of life and survivorship in general.

Although many studies have been conducted to shed light on defining an exact model of exercise that would most effectively benefit cancer prevention and treatment, for remains to be found for a specific type or frequency of exercise. The field offers a wide prospects for future research to define optimal exercise programs, especially for patients receiving breast cancer treatment and for breast cancer survivors.

Individual exercise programs constitute a field with an enormous research potential, given that different patients respond differently to various types of exercise. Hence, depending on the patient's characteristics, personality, fitness status, and level of disability, exercise programs can be specifically tailored to the patient's needs and preferences, thus meeting their fullest effectiveness.

Disclosure

The authors have stated that they have no conflict of interest.

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