Muscle Strength, Body Composition, and Physical Activity in Women Receiving Chemotherapy for Breast Cancer

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There is evidence to suggest that treatment of breast cancer with chemotherapy can induce metabolic changes in skeletal muscle. Women undergoing treatment for breast cancer with certain chemotherapeutic agents can experience declines in lean body mass and muscle strength and a subsequent increase in body weight. These alterations not only can lead to declines in physical function but also predispose women to weight-related chronic illness. Excess body weight may also play a role in the development or recurrence of breast cancer. There is evidence that physical exercise may improve body composition and enhance muscular endurance, flexibility, and quality of life (QOL) in women with breast cancer. While studies of aerobic, resistance, and combinations of aerobic and resistance exercise for women with breast cancer have been conducted, most studies employed supervised aerobic exercise sessions. Few studies have examined the role of resistance exercise or the combination of resistance and aerobic exercise in maintaining or increasing muscle strength while preserving lean body mass in this population. The relatively small sample sizes and short duration of physical activity interventions in previous studies make it difficult to detect dose responses to exercise training. Physical activity interventions with larger sample sizes and of longer duration are necessary to achieve long-term health outcomes. Physical activity interventions that include the older or more obese women with breast cancer are also needed, as this population may be at risk of functional decline and the development of chronic illness. Interventions appropriate for women treated for breast cancer who have comorbid disease are also needed. Newer, more intense chemotherapy regimens may differ in their effect on muscle strength and body composition. However, the role of physical activity during dose-dense chemotherapy protocols has not been established.

Keywords: breast cancer; muscle strength; body composition; physical activity

The role of exercise and physical activity in cancer prevention, recovery, and rehabilitation has been the focus of much recent literature. In terms of cancer prevention, physical activity and exercise have been touted as part of a healthy lifestyle that can reduce the incidence of obesity-related chronic illnesses, cancer, and cancer recurrence. However, the mechanism by which physical activity or exercise exerts its effect and the amount of activity necessary remains unknown. There is evidence that physical exercise may improve body composition and enhance muscular endurance, flexibility, and quality of life (QOL) in women with breast cancer. However, most studies of exercise and cancer survivorship have been limited by small sample sizes, similar cancer disease stages, the use of single-modality exercise regimens, and limited duration of follow-up. Investigations of breast cancer disease and treatment side effects on muscle strength and body composition have been limited. The purpose of this article is to examine the effects of breast cancer chemotherapy on skeletal muscle and body composition and to explore the role of physical activity as a means of ameliorating the negative effects of chemotherapy.

Effects of Breast Cancer Chemotherapy on Skeletal Muscle

Treatment for breast cancer often involves the administration of doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan) chemotherapy followed by a taxane such as paclitaxel (Taxol) or docetaxel (Taxotere) for women with high-risk or node-positive disease. Typically, this chemotherapy regimen consists of 4 cycles of doxorubicin and cyclophosphamide administered every 3 weeks for 4 cycles followed by paclitaxel or docetaxel administered every 3 weeks for an additional 4 cycles. Newer chemotherapy regimens with concurrent growth factor support have permitted this

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standard therapy to be given in a dose-dense fashion every 2 weeks. This change in clinical practice has allowed chemotherapy for the treatment of breast cancer to be condensed over a shortened time period of 4 versus 6 months.

During treatment for breast cancer, metabolic changes in the muscles can be expected with the administration of certain chemotherapeutic agents. There is direct and indirect evidence that doxorubicin is myotoxic to cardiac skeletal muscle causing myofibrillar loss in a dose-dependent manner. Following administration of doxorubicin, there is accumulation of the drug within cardiac skeletal muscle, resulting in cardiotoxicity secondary to iron-catalyzed free radical formation. It would seem reasonable to expect a similar myotoxic response on other skeletal muscle in the body; however, the effects of doxorubicin on generalized body skeletal muscle have not been fully elucidated.

The administration of high-dose cyclophosphamide has also been associated with myotoxicity, including rare cases of rhabdomyolysis. Currently, the use of taxanes following doxorubicin and cyclophosphamide therapy for breast cancer treatment is becoming increasingly common. Taxane preparations are known to induce a wide range of peripheral sensory neuropathy; thus, current chemotherapy protocols predispose women to both myotoxicity and neurotoxicity from these agents. These metabolic alterations ultimately reduce muscle force-generating capacity, leading to muscle weakness and functional decline. Declines in muscle strength can lead to muscle weakness and atrophy, precipitating functional impairment. Physical activity works to increase endurance, muscle strength, and flexibility. Physical activity performed during and/or following chemotherapy may prove beneficial in staving off muscle weakness and atrophy resulting from the consequences of cancer treatment.

**Body Composition and Breast Cancer**

In addition to the effect chemotherapy administration can exert on skeletal muscle, weight gain as a frequent consequence of therapy can have adverse effects because of loss of lean body tissue and resultant gain in body fat. The association of excess body weight and the subsequent development of breast cancer is the focus of several epidemiological studies. While the evidence is preliminary, there appears to be a strong association between waist-hip ratio and the amount of weight gained over a woman’s lifetime to the development of postmenopausal breast cancer. Investigations are also being conducted to determine the significance of weight gain after diagnosis and treatment for breast cancer. Weight gain remains a common problem among individuals receiving adjuvant chemotherapy for breast cancer and may influence both upper and lower extremity muscle strength. Women treated for breast cancer have an average weight gain of 4.5 kg, which directly influences body composition. Shapiro and Recht found that most premenopausal women treated for breast cancer with cyclophosphamide, methotrexate, and flurouracil gained an average of 2 to 6 kg. Less is known about the patterns of weight alterations with the use of doxorubicin and cyclophosphamide followed by taxanes, and additional research is needed.

Most weight is gained during breast cancer treatment, and excess weight is maintained after treatment is completed. The mechanism by which this occurs is not well understood. The weight gained among women treated for breast cancer represents an increase in body mass index (BMI), fat mass, and percentage body fat and a concomitant decline in lean body mass. Changes in body composition are further compounded by inactivity related to fatigue, a common treatment-induced side effect. Elevated levels of fatigue compounded by chemotherapy-mediated alterations in skeletal muscle and body composition predispose women to muscle atrophy and weakness. These alterations have the potential to adversely affect the ability of women to carry out activities of daily living and, particularly for older women, can affect the ability to live independently.

Weight gain is not only a source of distress but also an additional risk for the development of chronic illnesses such as cardiovascular disease, diabetes, hypertension, and orthopedic disorders. At present, women have less than a 20% chance of mortality from breast cancer, which makes health concerns related to the prevention of chronic diseases more imperative. In light of this fact, lifestyle management strategies aimed at weight control for women treated for breast cancer should include recommendations for nutritional counseling and physical activity.

Recent epidemiologic data have established a link between excess body weight and breast cancer development and subsequent recurrence. Goodwin et al conducted a prospective study of women with operable breast cancer. Findings from this study concluded that for women with a BMI of 20 to 25 kg/m², the risk of recurrent breast cancer was low. However, the risk of recurrence rose steadily with BMI levels increased beyond 25 kg/m². Patterns of weight gain or loss may be altered by newer dose-dense chemotherapy administration schedules. Changes in the delivery schedule of breast cancer chemotherapy from every 3 weeks to every 2 weeks may alter the sequence of alterations in body composition experienced by women. The adoption of dose-dense administration of...
4 cycles of doxorubicin/cyclophosphamide followed by an additional 4 cycles of paclitaxel may result in more severe nausea and vomiting during the acute treatment phase despite rigorous antiemetic dosing, resulting in initial loss of weight. However, the more common chemotherapy-induced menopausal side effects experienced, such as weight gain, may not be noted until after therapy is completed. At present, long-term follow-up data of weight loss or gains resulting from dose-dense schedules are lacking. Furthermore, there are limited data concerning the feasibility and efficacy of physical activity interventions during dose-dense chemotherapy for breast cancer.

Physical Activity and Breast Cancer

In recently published guidelines, the American Cancer Society’s recommendations concerning physical activity levels for cancer survivors who have completed treatment reflect the recommendations provided to the general public. Consequences of inactivity both during and following chemotherapy include muscle atrophy, osteopenia, declines in cardiorespiratory fitness, decreased insulin sensitivity, decreased immune function, and increased risk of chronic illness. While there is great interest in using physical activity to negate the deleterious side effects of chemotherapy, the American Cancer Society guidelines note that the safety of participating in routine physical activity for individuals who are under current cancer treatment has yet to be established. Regardless of physical activity modality, only 3 studies of physical activity focused exclusively on postmenopausal women with breast cancer, while the remaining studies enrolled both premenopausal and postmenopausal women. Most studies recognized the importance of frequency, intensity, and duration as an integral part of physical activity interventions. Frequency, intensity, and duration were specified in most studies, and a plan for increasing these parameters on an individual basis throughout the study was noted. When examining the effects of physical activity, the consequences of inactivity are also of great importance. A recent meta-analysis by Schmitz et al examining the effect of controlled physical activity in cancer survivors noted that inactivity both during and following cancer treatment can have ill effects on cardiorespiratory functioning, which in turn could negatively affect bone mineralization, muscle strength, glucose metabolism, insulin sensitivity, and digestive and immune functioning.

Aerobic Exercise

Both aerobic and resistance exercise target skeletal muscle to increase the ability to sustain submaximal exertion and increase muscle mass and force and provide additional benefits in terms of increasing lean body mass while reducing fat mass. To date, many studies of aerobic physical activity specifically targeted to women with breast cancer have been conducted. These 15 studies primarily enrolled women with early-stage breast cancer. Only a few studies have included women with stage III disease, beginning the process of generalizing exercise trial findings to more advanced disease states. To date, no clinical trials of physical activity specifically for women with breast cancer have included women with metastatic (stage IV) disease. The outcome measures in these studies primarily focused on physical functioning and symptoms such as nausea, depression, anxiety, sleep disturbances, fatigue, and emotional distress and, more recently, included biomarkers of immune function, cardiovascular risk, fasting insulin, insulin-like growth factors, and binding proteins.

All studies of physical activity reviewed used an aerobic exercise intervention in the form of walking or cycling. Several studies using supervised cycle ergometer exercise programs 3 times weekly for 10 to 15 weeks found that women with breast cancer who participated in the exercise program reported less symptoms such as nausea, emotional distress, increased functional capacity and VO2 max, decreased fat mass, and increased lean body mass as compared with the control groups. Aerobic exercise in the form of walking or cycling has also been used as an intervention to reduce fatigue and improve QOL. The findings of these studies suggest that women with breast cancer who engaged in aerobic exercise reported higher QOL as compared to those who did not exercise. Overall, the literature suggests that aerobic exercise both during and after treatment for breast cancer can improve physical functioning and QOL. However, less is known about the effects of aerobic exercise on maintaining skeletal muscle strength or on overall body composition parameters. As women survive longer with breast cancer, effective means of addressing the effects of therapy on physical performance and gains in body weight, fat mass, and percentage body fat are needed to prevent debilitation and the development of chronic diseases that result from these alterations.

Resistance Exercise

The benefits of resistance exercise or strength training have been well documented. Following resistance or strength training exercises, the cross-sectional area of the muscle hypertrophies as a result of increased synthesis of actin and myosin, resulting in reduced muscle fatigability. It is this accelerated rate of cellular protein synthesis in contracting muscles that increases muscle mass and thus muscle strength.
However, few studies have examined the effects of resistance or strength training exercise in individuals with cancer (see Table 1).\textsuperscript{25,42-46} One study examining the effects of resistance exercise in preventing skeletal muscle atrophy of bone marrow transplant recipients receiving total parenteral nutrition found that exercise induced a muscle protein-sparing effect.\textsuperscript{42} Study results may have been confounded by variations in baseline arm muscle area and nutrition protocols.

In a randomized clinical trial, Segal et al\textsuperscript{42} investigated the effects of a 12-week program of resistance exercise on fatigue, disease-specific QOL, muscular fitness, and body composition in 155 men receiving androgen deprivation therapy for prostate cancer. Men in the exercise group had less fatigue, better QOL, and higher levels of muscular fitness as compared to the control group. The 12-week resistance exercise program did not improve body composition. McKneely et al\textsuperscript{43} conducted a pilot study of progressive resistance exercise training (PRET) on shoulder dysfunction with 20 patients with squamous cell carcinoma of the head and neck. Study participants were randomized to receive standard care or the PRET intervention consisting of progressive increases in weight lifted and repetitions 3 times weekly for 12 weeks. The PRET group had significant improvement in external shoulder rotation, shoulder pain, and disability.

In a 12-month study of strength training in 85 breast cancer survivors, participants were randomized to immediate or delayed strength training intervention groups. Anthropometric measures (waist circumference, body weight, and height), physical activity, food and nutrient intake, fasting blood glucose, plasma insulin levels, insulin resistance, and insulin-like growth factors were completed at baseline arm muscle area and nutrition protocols.

Waltman et al\textsuperscript{46} tested a 12-month multicomponent intervention for preventing or treating osteoporosis in 21 postmenopausal breast cancer survivors. The intervention consisted of home-based strength and weight training exercises, 5 or 10 mg alendronate per day, 1500 mg calcium per day, 400 IU vitamin D per day, education on osteoporosis, and facilitative strategies to promote adherence to the intervention. Outcome measures were adherence to the intervention, dynamic balance, muscle strength, and bone mineral density (BMD) of the hip, spine, and forearm. Adherence to calcium, vitamin D, and alendronate therapy was greater than 95%, and exercise adherence was greater than 85%. Over the 12 months, the 21 participants had significant improvements in dynamic balance; muscle strength for hip flexion, hip extension, and knee flexion; and BMD of the spine and hip. Participants had a significant decrease in BMD of the forearm. Three of the 21 women who had measurable bone loss at baseline had normal BMD after 12 months of the intervention.

The few studies testing the effects of resistance exercise in women with breast cancer were conducted after the completion of cancer therapy, with the exception of long-term antiestrogen therapy. There is a dearth of knowledge about the effects of strength (resistance) exercise in women with breast cancer undergoing active cancer treatment. Resistance exercise appears not to induce or worsen lymphedema associated with surgical dissection of lymph nodes.\textsuperscript{46} As such, resistance exercise needs further exploration as a means of increasing muscle strength and assisting with the development of lean body mass for women with breast cancer.

**Combination Aerobic/Resistance Exercise**

Several studies tested the effects of both aerobic and resistive exercise in differing cancer populations (see Table 1).\textsuperscript{34,35,48-50} Specifically for women with breast cancer, Nieman et al\textsuperscript{48} examined the effects of a supervised walking and weight training program performed 3 times weekly for 8 weeks in 12 breast cancer survivors. Before and after measures of physical (aerobic performance, leg strength) and immune systems (concentrations of circulating lymphocyte subsets and natural killer cell cytotoxic activity) were collected. While the experimental group demonstrated decreased heart rate and increased 6-minute walk test and leg strength, no significant differences were found in natural killer cell activity.

Kolden et al\textsuperscript{34} conducted a 16-week pilot study of group exercise training (GET) for 40 sedentary women with breast cancer. All women had undergone breast cancer–related surgery and were concurrently receiving adjuvant treatment with radiation, chemotherapy,
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<th>Author, Year</th>
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<tr>
<td>Cunningham et al, 1986</td>
<td>30 patients with acute leukemia undergoing bone marrow transplant</td>
<td>Resistance exercise performed either 3 or 5 times weekly for 5 wk</td>
<td>Nitrogen balance, creatinine excretion, triceps skinfold, arm circumference, body weight</td>
<td>Decreased nitrogen balance, no effect on creatinine excretion or arm circumference</td>
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<td>Segal et al, 2003</td>
<td>155 men with prostate cancer</td>
<td>Resistance exercise program performed 3 times per wk for 12 wk</td>
<td>Muscular fitness, body composition, PSA levels, fatigue, QOL</td>
<td>42% increase in upper body fitness, 36% increase in lower body fitness; no change in body composition or PSA levels; decreased fatigue; increased health-related QOL</td>
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<tr>
<td>Waltman et al, 2003</td>
<td>21 postmenopausal breast cancer survivors</td>
<td>12-mo multicomponent intervention consisting of alendronate, calcium, vitamin D supplementation, and twice-weekly resistance exercises</td>
<td>Dynamic balance, muscle strength, bone mineral density of the spine, hip, and forearm</td>
<td>Significant improvements in dynamic balance, hip and knee flexion, hip extension, and hip and spine bone mineral density; bone mineral density of the forearm significantly decreased</td>
</tr>
<tr>
<td>McKnely et al, 2004</td>
<td>20 patients with head and neck cancer</td>
<td>Progressive resistance exercise program performed 3 times per wk for 12 wk</td>
<td>Shoulder function, pain and disability, QOL</td>
<td>Significantly improved shoulder external rotation, decreased overall shoulder pain, trend for improvement in shoulder disability; no effect on QOL</td>
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<tr>
<td>Schmitz et al, 2005</td>
<td>85 recent breast cancer survivors</td>
<td>Supervised progressive resistance exercise program performed twice weekly for 13 wk, followed by 13-wk independent training</td>
<td>Waist circumference, body weight, body fat, fat-free mass, bone density, fasting glucose, insulin, insulin resistance, insulin-like growth factors (IGF-1, IGF-2), IGF binding protein 1 and 2</td>
<td>Significant increases in lean body mass, significantly decreases in body fat percentage and IGF-2; no change in insulin, glucose, or IGF-axis proteins</td>
</tr>
<tr>
<td>Ohira et al, 2006</td>
<td>86 breast cancer survivors</td>
<td>Supervised progressive resistance exercise program performed twice weekly for 13 wk, followed by 13-wk independent training</td>
<td>QOL (physical, psychosocial, medical interaction, marital, sexual, miscellaneous), depressive symptoms, waist circumference, body weight, body fat, fat-free mass, bone density, upper and lower body strength</td>
<td>Improved global QOL; significantly improved psychosocial global score; no change in depressive symptoms. Increased upper body strength and lean body mass was correlated with improved physical global score and psychological global score</td>
</tr>
<tr>
<td>Nieman et al, 1995</td>
<td>12 breast cancer survivors</td>
<td>Combination aerobic/resistance exercise program performed 3 times weekly for 8 wk</td>
<td>Physical performance, immunological training response</td>
<td>Significant improvements in physical performance as measured by the 6-min walk test; no effect on lower body strength or natural killer cell cytotoxic activity</td>
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<tr>
<td>Porock et al, 2000</td>
<td>9 patients with advanced cancer (bowel, breast, oral, pancreas, melanoma)</td>
<td>Combination aerobic/resistance exercise program performed for 28 d (frequency of exercise not described)</td>
<td>Fatigue, depression, anxiety</td>
<td>Decreased depression and anxiety; no effect on fatigue levels</td>
</tr>
<tr>
<td>Kolden et al, 2002</td>
<td>40 breast cancer survivors</td>
<td>Combination aerobic/resistance exercise program performed 3 times weekly for 16 wk</td>
<td>Physical capacity, physical activity level, psychosocial well-being</td>
<td>Significant increases in fitness/vigor; increases in strength, aerobic capacity, and QOL</td>
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<td>Adamsen et al, 2003</td>
<td>23 patients with advanced cancer (leukemia, lymphoma, breast, colon, gynecologic, testicular)</td>
<td>Multidimensional program of combination aerobic and resistance exercise (high and low intensity), relaxation, massage, and body awareness training performed 4 times weekly for 6 wk</td>
<td>Fitness, lymphocyte activation, activated cytokines</td>
<td>32.5% increase in whole-body strength, 16% increase in maximal oxygen uptake; no effect on QOL</td>
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<td>Hutnick et al, 2005</td>
<td>49 women with breast cancer scheduled for or receiving chemotherapy</td>
<td>Combination aerobic/resistance exercise program performed 3 times weekly for 6 mo</td>
<td>Fitness/vigor, body weight, body fat, aerobic capacity, strength, flexibility, and QOL</td>
<td>Increased maximal oxygen uptake and upper body strength, increased CD4+, CD69+ T helper cells, increased tritiated thymidine incorporation; no differences in cytokine concentration or production</td>
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PSA = prostate-specific antigen; QOL = quality of life.
or hormonal therapy. Women met as a group 3 times weekly for a structured exercise program consisting of warm up, aerobic training, resistance training, and a cool down. Measures of fitness, strength, flexibility, and QOL were taken at baseline, during the study, and following the completion of the study. Results demonstrated increases in strength, flexibility, aerobic capacity, and QOL. The GET intervention was feasible, safe, and well tolerated.

A randomized clinical trial by Hutnick et al\textsuperscript{55} investigated the use of a structured, 3-times-weekly, 6-month exercise program consisting of stretching, aerobic treadmill-based exercise, and resistance exercises using Flexbands (Jumpstretch Inc, Boardman, Ohio) on lymphocyte activation for 28 women with breast cancer scheduled for or receiving treatment with chemotherapy. Results showed that the exercise group had increased maximal oxygen uptake and upper body strength as compared to the control group (n = 21). Exercise participants also had a greater percentage of CD4+ and CD69+ cells and greater tritiated thymidine incorporation. However, plasma and mitogen-stimulated cytokine (interleukin-6, and interferon-γ) production was similar in both groups.

Because of the ability of aerobic exercise to improve cardiorespiratory fitness, burn calories, reduce heart rate, and reduce blood pressure, combining this modality with resistance or strength training exercises that can increase muscle strength and endurance and increase lean body mass may provide the best overall health and physical functioning benefits for women with breast cancer.

**Future Directions**

While relatively small sample sizes in studies of breast cancer and physical activity make generalizations to the population difficult at best, the very low numbers of older women in these studies (>65 years) need to be addressed. The aging process is associated with decreases in muscle mass, flexibility, and QOL. The GET intervention was feasible, safe, and well tolerated.

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Because of the ability of aerobic exercise to improve cardiorespiratory fitness, burn calories, reduce heart rate, and reduce blood pressure, combining this modality with resistance or strength training exercises that can increase muscle strength and endurance and increase lean body mass may provide the best overall health and physical functioning benefits for women with breast cancer.

It is notable that most physical activity interventions for women with breast cancer employed a cardiovascular fitness approach. Few studies have incorporated resistance or strength training as a physical activity modality. Segal et al\textsuperscript{54} reported decreased fatigue, increased health-related QOL, and increased muscle strength in men undergoing androgen deprivation therapy for prostate cancer with resistance exercises. Considering the health implications of weight gain for women with breast cancer, future research will need to explore how resistance or strength training exercises during or after treatment can affect long-term muscle strength and body composition in this population. Furthermore, with the advent of aromatase inhibitor therapy for postmenopausal women with breast cancer, the negative side effect of osteoporosis becomes of particular concern. Resistance exercise plus vitamin D and calcium supplementation may have a role in increasing BMD and preventing fractures. At present, the role of resistance exercise in preventing fractures in women with breast cancer who are at risk of bone metastasis is not known.

Earlier work by Chlebowski et al\textsuperscript{54} and Goodwin et al\textsuperscript{55} suggests that interventions should be aimed at the prevention of weight gain during treatment, as opposed to weight reduction strategies that begin at the end of treatment. Early clinical assessment of excess weight at diagnosis should prompt clinicians to develop nutrition- and activity-based strategies to assist with weight reduction. Encouraging even modest physical activity throughout the treatment trajectory could preserve baseline muscle strength, preventing the need for rehabilitation following treatment.

For reasons of safety, physical activity interventions for women with breast cancer typically excluded the obese (BMI >35-40 kg/m\textsuperscript{2}) and those with preexisting cardiopulmonary conditions, such as hypertension. While safety is indeed a concern, exclusion of those with obesity and comorbid conditions bars women most in need of the health benefits associated with physical activity. Safe, feasible interventions are needed for older women who have comorbid illness in addition to their primary breast cancer diagnosis.

Finally, clinical trials of physical activity in women with breast cancer have been of relatively short duration and thus the ability to detect dose responses to exercise training. Longer term studies are needed to fully understand the physiological responses in a cancer as opposed to a healthy population. The optimum modality or combination of exercises and the frequency, intensity, and duration of physical activity needed to increase or maintain muscle strength to positively affect body composition and provide the greatest health benefits remain unknown.
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