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Should resistance exercise be recommended during breast cancer treatment?

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SUMMARY

Epidemiological evidence has pointed to the benefits of physical activity in reducing breast cancer risk, which in turn has prompted the American Cancer Society (ACS) to make specific recommendations for adopting a life style of physical activity as a guideline for cancer protection. There is also evidence for benefits of physical activity during and after cancer treatments of chemotherapy and radiation therapy. The ACS recommendations for exercise as prevention and for exercise during/after cancer treatment are the same: "that adults engage in at least 30 min of moderate to vigorous physical activity, above usual activities, on 5 or more days of the week; 45–60 min of intentional physical activity are preferable." These recommendations suggest participation in aerobic types of physical activity (e.g. brisk walking, biking). Effects of resistance exercise were not addressed specifically by the ACS but have been found to increase lean body mass in patients undergoing cancer treatment. Also, many women preferred resistance exercise over aerobic exercise during breast cancer treatment. In response to strenuous resistance exercise, however, muscle satellite (progenitor) cells are activated to reenter the cell cycle and proliferate. Satellite cells can then contribute their nuclear material into the fiber to facilitate muscle repair, regeneration, and hypertrophy. Cancer therapy damages rapidly dividing cells and thus has the potential to target satellite cells that enter into the cell cycle. Although satellite cells are self-renewing, they are not completely replenished over the lifespan so losses in this progenitor population via resistance exercise and cancer therapy may impair the maintenance of muscle mass with aging. Before recommending resistance training during breast cancer treatment, we must have more information about cancer treatment effects on activated satellite cells in human studies.

Introduction

In 2009, the American Cancer Society (ACS) estimated that there were 192,370 new breast cancer cases and 40,170 deaths, making breast cancer the leading number of new cancer cases for women and the 2nd most common cause of cancer death [1]. The high incidence of breast cancer has stimulated research on factors that reduce the probability of developing, and increase the success in treating, this disease. Modifiable risk factors include alcohol consumption, dietary intake, physical activity, and body weight [2]. Within the last decade, much epidemiological evidence has pointed to the benefits of physical activity in reducing breast cancer risk, which in turn has prompted the ACS to make specific recommendations for adopting a life style of physical activity as a guideline for cancer protection [3].

Participation in physical activity after breast cancer treatment has also been significantly associated with a reduction in the risk of death from this disease [4]. Moreover, attention has been paid to the potential benefit of physical activity during cancer treatment [5,6]. Chemotherapy and radiation therapy are commonly associated with fatigue [7], which could lead to a downward spiral of reducing physical fitness, functional capacity, and quality of life. Mock et al. [8] found that a home-based walking program during adjuvant chemotherapy or radiation therapy appeared to mitigate fatigue experienced during cancer treatment.

The ACS recommendations for exercise during and after cancer treatment are the same as for reducing the risk of developing breast cancer [5]. The specific recommendation is: "that adults engage in at least 30 min of moderate to vigorous physical activity, above usual activities, on 5 or more days of the week; 45–60 min of intentional physical activity are preferable" [3,5]. These recommendations suggest participation in aerobic types of physical activity (e.g. brisk walking, biking). Effects of resistance exercise were not addressed by the ACS but have been recently examined in patients undergoing cancer treatment. However, here we present evidence to suggest that further studies are warranted before resistance exercise is recommended for cancer patients undergoing cancer therapy. Specifically, more information is needed regarding the effects of initial chemotherapy and radiation therapy on muscle satellite (progenitor) cells that are activated to proliferate in response to resistance exercise.

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Resistance exercise during cancer treatment

Courneya et al. [9] conducted a multicenter randomized control trial where 242 breast cancer patients initiating adjuvant chemotherapy participated in either a supervised resistance exercise or aerobic exercise training regimen for 17 weeks. Although the exercise training did not significantly improve cancer-specific quality of life measures, there were improvements in self-esteem, physical fitness, and body composition. Resistance exercise specifically improved muscular strength and total lean body mass. Furthermore, this study found that patients who had a preference for either resistance or aerobic exercise benefited more by being placed into the exercise training group they preferred [10]. Recently, Mustian et al. [11] examined the effect of a 4 week home-based combined aerobic and resistance exercise program in breast and prostate cancer patients beginning radiation therapy. Both exercises were performed 7 days/week. The aerobic exercise consisted of walking program, and the resistance exercise was designed as a low to moderate intensity exercise using therapeutic resistance bands. The exercise group compared to a control group, showed improvements in fatigue scores and higher quality of life measures. Arm swelling was also assessed in the Courneya et al. [9] study to investigate whether the side effect of lymphedema in breast cancer patients was exacerbated by exercise. Although it was once thought that resistance exercise may increase the risk of lymphedema, the results of Courneya et al. and others suggest otherwise [9,12].

The existing evidence shows that exercise participation during cancer treatment is safe, feasible, and can provide some health advantage. However, there is insufficient information available to define the mechanistic basis for any potential benefit of exercise in reducing fatigue during cancer therapy or decreasing cancer risk. One animal study found that aerobic exercise training during doxorubicin chemotherapy did not influence tumor growth delay in mice carrying xenografts of human MDA-MB-231 breast cancer cell derived tumors [13]. In the American Cancer Society Guide for informed choice, Doyle et al. [5] state that ‘‘Although there is not a strong biological rationale for concern about adverse effects of exercise during treatment, research into this question is needed.” While we agree that research is needed, we propose that there is a biological rationale for concern that performance of resistance exercise during cancer therapy potentially may be harmful.

Cancer therapy

All cells carry the molecular machinery for committing suicide, a process known as apoptosis. DNA-induced cellular damage, either through ionizing radiation or some chemotherapeutic drugs, is one of the key triggers for apoptosis, and actively dividing cells are far more sensitive to these insults than are ones that are quiescent or differentiated, such as neurons. This is why gastrointestinal side effects in response to radiation or chemotherapy occur more quickly and with lower doses than neurological complications.

Chemotherapeutic drugs can disrupt the cell cycle at several critical steps and thereby induce apoptosis. For example: *taxane drugs* work to bind to and stabilize cell microtubules to prevent them from separating chromosomes during cell division (anaphase of mitosis), thereby arresting the cell cycle; *doxorubicin* (*adriamycin*) prevents DNA replication by inhibiting the enzymes, topoisomerases, that cut one strand of DNA to unwind it during replication; and *5-fluorouracil* (*5FU, adrucil*) inhibits thymidylate synthetase that functions to incorporate the thymine nucleotide into DNA during replication. Some of the more rapidly dividing normal, healthy cells are damaged (e.g. hair follicles, blood cells), subsequent mitosis from resident stem cells can soon replace those lost to chemotherapy or radiation.

The tumor suppressor protein p53 is required for most DNA-damage-induced apoptosis. Unfortunately mutations in the p53 gene are observed in upwards of 70% of human cancers, thus reducing the efficacy of some therapies [14]. After surgery to remove a tumor (lumpectomy or mastectomy), high levels of ionizing radiation are used to destroy any remaining breast cancer cells in the breast, chest wall, or axilla area. Cell death from radiotherapy occurs primarily during mitosis, when extensive DNA damage makes duplication of the genome impossible (mitotic cell death). p53-Dependent apoptosis occurs at the G1 checkpoint of the cell cycle and helps ensure that DNA carrying genomic defects are not replicated. However, in the absence of p53, or when p53 is non-functional, the cells become insensitive to low dose radiation. Instead, high doses are required to functionally damage the cell and induce necrosis [15]. In contrast to apoptosis, necrosis releases cytoplasmic constituents into the surrounding tissue, which serve as potent inflammatory signals [16]. Recent evidence suggests that the fatigue experienced with radiation therapy is associated with the activation of proinflammatory cytokines [17].

Resistance exercise and satellite cells

Muscle fibers are multinucleated cells providing a nuclear domain for directing protein synthesis to meet the protein demands for maintenance, regeneration, and repair of actively contracting fibers. In addition, each fiber contains a pool of satellite, or progenitor, cells located between the sarcolemma and basement membrane of muscle fibers, which are quiescent in adult muscle unless they are activated [18]. Evidence in both animal and human studies shows that tension and stretch overload and release of inflammatory substances or growth factors produced by resistance exercise activate satellite cells stimulating them to reenter the cell cycle and proliferate [18–24]. Satellite cells can then contribute their nuclear material into the fiber to facilitate muscle repair, regeneration, and hypertrophy in response to overload [25]. A subset of activated satellite cells replace themselves and then exit the cell cycle so that they are available in the future for muscle repair [26]. Thus, not only do satellite cells proliferate to contribute nuclear material to the muscle fiber, they also are self-renewing [26]. However, the ability to expand the number of satellite cells in response to overload exercise is impaired in older individuals, thus contributing to the regenerative deficits in the elderly [27]. A similar process is observed in children with Duchenne Muscular Dystrophy, where repeated round of muscle damage and repair exhaust the satellite pool [28].

Radiation is commonly used in muscle research to induce DNA damage in satellite cells and their subsequent death. (The mature muscles themselves are very radio-resistant and do not appear to be impacted by this treatment). Typically, one or more doses of gamma radiation of 1800–3000 rads (18–30 Gy) are used to ablate the satellite cell population [24,29]. Muscle irradiation has been shown to prevent muscle fiber regeneration in response to muscle damage due to suppression of satellite cell proliferation [24,30].

Should resistance exercise be recommended during cancer therapy?

Courneya et al. [10] queried 242 breast cancer patients beginning adjuvant chemotherapy regarding their preference for resistance exercise or aerobic exercise. Of the participants, 40.9% preferred the resistance exercise, 36.4% preferred aerobic, and 22.7% reported no preference. The relatively large percentage of women preferring resistance exercise may be explained by a perception that they would gain more benefit from resistance training. These women were likely facing surgery that would leave their

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upper body weak and disfigured, so increasing muscle mass and strength in the chest area would be appealing. Thus, a high percentage of women with breast cancer may opt to begin a resistance exercise program as more physicians recommend exercise to their patients.

In one study cited above [9], resistance exercise performed during chemotherapy did have the benefit of increasing lean body weight. This may suggest that satellite cells were activated to increase the fibers' nuclear domain thereby meeting the demands of increased protein synthesis. However, do these exercises sensitize some satellite cells to destruction, which will lower the number of muscle progenitor cells available for subsequent muscle maintenance and repair? Information is needed on the extent of satellite cell activation during resistance exercise in humans and the effect of chemotherapy on these activated cells. It is possible that the protracted time between cycles of chemotherapy (doses every 3–4 weeks) reduces significant satellite cell destruction.

During radiation therapy for breast cancer, the muscles of the chest wall may be irradiated. These muscles include the pectoralis (major and minor), subclavius, and serratus anterior. Depending on the radiation treatment area, muscles of the back, particularly the rhomboid layer and underlying deep muscles, may be exposed to radiation as well. Common resistance exercises, like the bench press, push-ups, chin-ups, and lat pull-downs, involve these chest wall and back muscles.

A typical radiation dose used in breast cancer treatment is 1.8–2.0 Gy/day, 5 days/week, over 6 weeks (total of about 54–60 Gy); this total dose is similar to what has been used to ablate satellite cells in animal models. Performance of high force resistance exercise, which increases load and stretch on the muscle, activates the satellite cells causing them to enter the cell cycle potentially exposing them to destruction by radiation. Ablating satellite cells will deplete the muscle of it progenitor cell pool.

Satellite cells are not fully replenished throughout life leading to reduced muscle regenerative capability during normal aging [31]. Resistance exercise performed during cancer therapy may, in theory, accelerate this decline, which may have profound consequences for sarcopenia in women who have undergone cancer therapy. Particularly, during radiation treatment for breast cancer, the chest and back muscles may be vulnerable.

Conclusion

Cancer therapy damages rapidly dividing cells and thus has the potential to target satellite cells that enter into the cell cycle. Satellite cells are not completely replenished over the lifespan so losses in this progenitor population can impair the maintenance of muscle mass with aging. Certainly, participation in exercise lowers the risk of a breast cancer diagnosis, and there is a growing body of evidence that it has beneficial effects during and post-treatment. Data on aerobic exercise are particularly strong. However, many women may prefer resistance exercise during breast cancer treatment [10], likely because this form of exercise will build muscle mass and strength to the weakened upper body. What has not been addressed is whether there could be a negative effect of resistance exercise during cancer therapy because it stimulates satellite cell activation and proliferation. There are no data regarding a dose–response for the intensity of resistance exercise that will activate satellite cells in human muscle. Likely, high force low repetition contractions will, and low force high repetition contractions will not. Also, there are no data to show that the chemotherapy or radiation dose used to treat breast cancer will negatively impact the satellite cell pool. Before recommending resistance training during breast cancer treatment, we must have more information about cancer treatment effects on activated satellite cells in human studies.

Conflicts of interest statement

None declared.

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