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Exercise as a Preventative Measure in Women with BRCA Gene Mutations

Karen Y. Wonders*

Ph.D., FACSM, Department of Kinesiology and Health, Wright State University, Dayton, OH; Maple Tree Cancer Alliance, Dayton, OH

Brittany Stout

Maple Tree Cancer Alliance, Dayton, OH

Abstract: Women who test positive for one of the two breast cancer susceptibility genes, BRCA1 and BRCA2, increase their risk by 45-55 percent. Currently, there are no specific physical activity recommendations for these women. However, research supports the positive effect of exercise on reducing breast cancer risk by reducing BMI, adipose tissue, and damage caused by lipid peroxidation.

Keywords: Exercise as a preventative measure, Potential mechanisms, BRCA Gene Mutations.

1. Introduction

Approximately one out of every 8 women is at risk for developing breast cancer in their lifetime [1]. However, women who test positive for one of the two breast cancer susceptibility genes, BRCA1 and BRCA2, increase their risk by 45-55 percent [2]. BRCA1 and BRCA2 genes are responsible for producing tumor suppressor proteins within the body. Under normal conditions, these proteins protect against tumor formation by helping to repair damaged DNA and protect the cell's genetic material. However, if the BRCA gene is mutated, the stability of the cell's genetic information is threatened, making it susceptible to cancerous genetic alterations [2]. Traditional strategies employed to reduce cancer risk in BRCA-positive women often include preventive surgery, hormone therapy, and more frequent cancer screenings [3]. However, recent research has examined the role of exercise as an effective preventative measure in women who test positive for the BRCA gene mutation. This review aims to examine this literature, and attempts to identify various mechanisms behind its protective effects.

2. Exercise as a Preventative Measure

Physical activity and exercise are preventive and rehabilitative measures that can be introduced at various points along the breast cancer trajectory. Clinicians are encouraged to assess the physical activity level of breast cancer patients and to educate them on the potential benefits of exercise, prior to, during and following treatment. In a review of 44 studies that examined the association between physical activity and breast cancer, 32 supported a 30-40% reduction in breast cancer risk among women who were physically active [4]. The specific dose of exercise necessary to infer a risk reduction has yet to be determined; however, many studies suggest that a moderate level of physical activity plays a key role in primary prevention against breast cancer [5-9]. One investigation [7] reviewed 21 studies on physical activity and breast cancer. Of these 21 cases, 15 (71%) suggested physical activity reduced breast cancer risk. In addition, Gammon, *et al.* [8] reported a 12-60% risk reduction among pre- and post-menopausal women who exercised. Worth noting are inconsistencies observed at different time periods of a woman's life. Friedenreich, *et al.* [10], examined breast cancer risk associated with lifetime recreational, household, and occupational activities separately and in combination. While no association was made between lifetime activity and breast cancer risk in pre-menopausal women, it was found to reduce breast cancer risk in post-menopausal women. Interestingly, household and occupational activities were associated with the largest risk reductions in this group.

Currently, no scientific consensus exists on the appropriate intensity, duration, or frequency of exercise needed to influence breast cancer risk. Bernstein, *et al.* [5] reported a strong reduction in breast cancer risk in a study of women under the age of 40. In this investigation, subjects completed a detailed physical activity assessment instrument that quantified the average number of hours per week women spent doing recreational physical activity. According to the data analysis, it was determined that an average of 3.8 hours or more of physical activity per week was associated with the greatest reductions in breast cancer risk. Likewise, Rockhill, *et al.* [11] reported that women between the ages of 30 and 55 who were more physically active had a lower risk of breast cancer than those who were less physically active. Specifically, women who reported engaging in moderate or vigorous physical activity

for at least 7 hours each week had a relative risk of 0.82, compared to those who reported engaging in physical activity for less than 1 hour per week.

3. Potential Mechanisms for Reducing Breast Cancer Risk through Exercise

The underlying mechanism contributing to the risk reduction of breast cancer associated with exercise is unclear. It is possible that there is a connection between body size and fat stores [12-15]. Recently, a study performed on breast cancer survivors suggested that non-hormonal factors, such as physical activity, might play a role in mediating body size [16]. An increased body mass index (BMI) has been linked to increased inflammation and levels of insulin and insulin-like growth factors, all of which are associated with breast cancer risk [16]. To support this, a recent study reported an inverse relationship between breast cancer risk and physical activity [17, 18]. Moreover, a positive relationship has been found between the rates of breast cancer diagnoses and BMI in women who were not on hormone therapy [16].

Regular exercise is often associated with a reduction in body fat, which leads to reduced substrate for the production of estrogen from androstenedione in fat tissue [15]. In addition, exercise may also increase levels of sex hormone-binding globulin, thereby reducing the amount of estradiol [14]. Therefore, it is possible that exercise reduces breast cancer risk by lowering a woman's exposure to estrogen. This is supported by a recent meta-analysis, which reported a modest, but not significant, risk reduction of breast cancer in women who are physically active [16].

Another possible mechanism may involve lipid peroxidation and the production of reactive oxygen species (ROS). Numerous studies have suggested that exercise causes the production of lipid peroxidation. Aerobic metabolism is dependent on oxidative phosphorylation, a process whereby ATP is formed through mitochondrial electron transport. The mitochondrial electron transport system involves the sequential transfer of electrons through a series of oxidation/reduction reactions. Cytochrome c oxidase serves as the final electron acceptor for this system; and, under normal conditions, reduces oxygen to water. However, intermediate proteins in the mitochondrial electron transport system are not always entirely efficient in the transfer of electrons, and occasionally may release electrons directly to oxygen. This results in the formation of ROS, partially reduced and highly reactive metabolites of oxygen [19]. Therefore, increases in oxygen consumption observed during exercise are accompanied by a concomitant increase in ROS. ROS cause damage by binding to proteins, lipids, and nucleic acids, thereby altering their conformation and function [20, 21].

The body is equipped with an antioxidant system to minimize damage caused by oxidative stress. Three enzymatic antioxidants in this system include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). SOD catalyzes the dismutation of $O_2^{\bullet -}$ to H_2O_2 and O_2 [22]. CAT catalyzes the reduction of H_2O_2 to water and $\frac{1}{2} O_2$. GPx is located in the cytoplasm and mitochondria of cardiomyocytes and uses glutathione (GSH) as a substrate to reduce H_2O_2 to water [23]. GSH is primarily synthesized by the liver and is transported to tissues via blood circulation, and is thought to play a critical role in protecting against oxidative stress, in that it can neutralize free radicals by donating two electrons [24].

If the amount of ROS exceeds the cell's antioxidant capacity, a state of oxidative stress results, initiating a cascade of events leading to lipid peroxidation, DNA damage, and apoptosis [25, 26]. Apoptosis is a highly regulated chemical form of programmed cell death. The complex process by which apoptosis induces cellular death involves four distinct phases; a stimulus phase, a signal transduction phase, a degradation phase, and a clearance phase. The stimulation phase involves a mechanism of stimulation to activate the relevant genetic machinery allowing the cell to begin apoptosis [27].

Free radicals are one such stimulus that modulates apoptosis [26]. It is possible that exercise may induce oxidative stress and subsequent apoptosis of pre-malignant and malignant cells of the breast, and thus protect against breast cancer. This hypothesis was tested by Radak, *et al.* [28], in an animal model. In this investigation, a decrease in tumor size was associated with an increase in levels of lipid peroxidation in animals who exercised both before and during tumor transplantation ($p < 0.05$).

4. Conclusions

Currently, there are no specific physical activity recommendations for women who test positive for the BRCA gene. However, research supports the positive effect of exercise on reducing breast cancer risk by reducing BMI, adipose tissue, and damage caused by lipid peroxidation.

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