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Physical activity and maximal aerobic capacity in breast cancer survivors – why this is important

Fizička aktivnost i maksimalna aerobna sposobnost kod žena koje su lečene od raka dojke – zašto je to važno

Zorica Brdareski*†, Aleksandar Đurović*†, Snežana Šušnjar‡, Mirjana Životić-Vanović†, Anđelka Ristić§†, Ljubica Konstantinović‖, Ljiljana Vučković-Dekić‡, Mirjana Tankosić¶

***Clinic for Physical Medicine and Rehabilitation, §Clinic for Emergency Internal Medicine, ¶Clinic for Haemathology, Military Medical Academy, Belgrade, Serbia; †Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia; ‡Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; ‖Clinic for Physical Medicine and Rehabilitation "dr M. Zotović", Belgrade, Serbia**

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Introduction

Breast cancer (BC) is the most frequent females' malignant solid tumor in Serbia and the leading cause of death from malignant disease among them [1, 2]. Although the number of new breast cancer patients is constantly rising, thanks to early diagnosis and modern methods of treatment, the number of successfully treated patients is growing, too. Treatment of malignant diseases is associated with numerous adverse effects – physical, mental, emotional and social. Unfortunately, these reactions are often not limited to the period of treatment, but are retained for months, even years after the treatment.

Different modalities of exercise therapy, aerobic training and physical activity in general, have for long been proven as significant factor and strong nonpharmacological tool in the fight against unwanted consequences of malignant disease and its treatment.

During chemotherapy and radiotherapy, the unsuspicious influence of aerobic training on aerobic capacity (VO_2max) and functional ability was demonstrated [3, 4]. It was also shown that aerobic training helps to control the side effects of treatment[5-7], may assist the modulation of level and pattern of daily fatigue [3, 8, 9] even in women with advanced disease [10], and can reduce the symptoms of psychological distress – anxiety, depression and sleep disorders [3, 8, 11]. Resistance exercises, alone or in combination with aerobic training, can improve muscle strength [12–15] and cause the change in body weight and body mass index [16, 17], reduce body fat [13, 15] and increase bone density [18]. It was also shown that such training can enhance adaptive responses to stress and improve quality of life of these persons [12].

Many papers report that aerobic and combined training given after therapy for breast cancer increase aerobic fitness, improve physical fitness [19–24] and increase strength and muscle elasticity [24, 25]. It was shown that such trainings can have a positive effect on fatigue [22, 26, 27], depression [21, 28], and the general quality of life [19–21, 29–31]. Resistance exercises of moderate level can be useful in the treatment of chronic lymphedema [32, 33].

Most importantly, there are growing body of evidence that regular moderate aerobic physical activity reduce the risk of relapse and significantly prolongs overall survival of breast cancer survivors (BCS) [34, 35]. This paper discusses the importance of primarily aerobic physical activity in terms of reducing the risk of relapse and impact on survival of these patients, and possible mechanisms underlying these effects, as well.

Definitions

Physical activity. It represents any movement of the body as a result of activity of skeletal muscles which substantially increases energy expenditure above basal levels (at least, 50% of maximum capacity for work or exercise) [36]. There are two main types of physical activities – aerobic, which increase aerobic capacity (walking, jogging, cycling, swimming, hiking) and non-aerobic, which increase muscle

Correspondence to: Zorica Brdareski, Clinic for Physical Medicine and Rehabilitation, Military Medical Academy, Crnotravska 17, 11000 Belgrade, Serbia. E-mail: zbrdareski@yahoo.com

strength, elasticity and endurance, but not the aerobic capacity (exercise with resistance, stretching, yoga). In recent years, besides sports and recreational activities, usually performed in leisure time, physical activities also includes occupational and household tasks [37, 38].

Exercise – It is planned, ordered, purposeful and repetitive physical activity, performed with the aim of preserving or improving physical fitness [39].

Physical fitness – It is defined as a set of properties that people have or achieve by performing physical activity [40]. There are the four general categories of measurement of physical activity: calorimetry, physiological markers, motion detectors and questionnaires. The last ones are the most popular and practical approaches for large groups of individuals. A compendium of physical activities has been developed to provide researchers and practitioners with an estimation of the energy cost for a wide variety of human physical activities [37, 41].

Metabolic equivalent (MET) – MET is a unit used to express metabolic cost (oxygen consumption) of physical activity. One MET is the metabolic oxygen consumption in peace (at baseline) and it is equal to 3.5 mL O_2/kg/min. The metabolic cost of an activity expressed in MET indicates how many times is oxygen consumption higher during these activities in relation to consumption in peace [37].

Aerobic capacity – It is the ability of the organism to create the energy required for execution of any work with an aerobic process. It is measured by the amount of oxygen consumed during the performance of such work.

Maximal aerobic uptake (VO_2max) – VO_2max is the amount of oxygen consumed during the work of maximal intensity. As a measure of aerobic capacity, it was established as an international standard for physical fitness. It depends on gender, age and genetic heritage, but also on the level of aerobic physical activity [39, 42]. Today VO_2max is accepted as a predictor of mortality from cardiovascular disease and mortality of all causes of death, both in healthy populations and patients with different chronic diseases (diabetes, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease), and smokers and obese persons, as well [43–45].

Body mass index (BMI) – BMI is the ratio between body weight and body height squared and expressed in kg/m^2. The normal BMI ranges between 18.5 and 25 kg/m^2. This is one of the widely accepted methods of obesity assessment [37].

Cancer survivor – It is any individual that has been diagnosed with cancer, from the time of diagnosis and for the balance of life [46]. This paper deals with women who have completed initial treatment for BC and have no apparent evidence of active disease.

Physical activity and body mass in women treated for breast cancer

Reduction of physical activity and increase of the body fat and body weight in breast cancer survivors (BCS) are two important risk factors for health. They are important not only for relapse of disease, but also for the morbidity from other chronic diseases such as arteriosclerosis, heart disease and diabetes. Although the risk of death due to primary disease remains elevated even 20 years after the diagnosis of breast cancer, the number of patients who die from other causes, such as cardiovascular disease is increasing [47].

According to the report of the International Agency for Research Cancer (IARC), about 25% of malignant diseases are the result of excessive weight and lack of physical activity [48]. Therefore, physical activity of these patients is of enormous importance. Yet, most patients diagnosed with malignant disease significantly reduce the extent and intensity of physical activity after the diagnosis compared to the period before the diagnosis.

Women with breast cancer are not an exception [49]. Taking into account antineoplastic therapy induced adverse events such as pain, nausea and fatigue, this trend is expected, although research shows that physical activity can help overcome these problems [8, 9, 50, 51].

In the Health, Eating, Activity, and Lifestyle (HEAL) multicenter study, conducted from July 1996 to March 1999, 1,185 women were enrolled 4–12 months after diagnosis of breast cancer. Among other objectives, the change of physical activity level of BCS after and before BC diagnosis was investigated and its impact on prognosis of the disease, as well. Data on physical activity were collected through a Modifiable Activity Questionnaire [52], and the average level of activity expressed in hours on a weekly basis. Authors analyzed 29 different activities (recreational and home activities) in addition to the time spent without the activity (reading, watching television, naps). Data were collected for two time periods – the period of 1 year before diagnosis and during the last month before the time of filling out questionnaires. A total of 812 women completed the study. It was shown that 52% of women with carcinoma *in situ*, 58% of women with locally and 62% with loco-regionally advanced disease reduced their overall level of physical activity. On average, an overall level of physical activity was decreased by 11%, corresponding to 2 hours *per* week, compared to the period before diagnosis. There was a significantly positive correlation between the type and intensity of physical activity and stage of the disease. Women with carcinoma *in situ* significantly reduced participation in sports / recreational and strenuous physical activities (≥ 6 MET), while women with locally or regionally advanced BC reduced the level of moderate activity (3–6 MET). The type of therapy is another factor that influenced the level of activity reduction. Women who had only surgery or radiotherapy were more active than those who received chemotherapy or combination therapy. It was also observed that the degree of obesity, expressed in BMI, is a good predictive factor for the level of physical activity. Overweight women had much more reduced activity (41.4%) than those whose BMI values were within normal limits (24.1%) or slightly higher than that (35.7%) [53].

Unfortunately, this trend of reducing physical activity continued in a follow-up period after initial treatment. Two years after the first interviews (within the third year of follow-up period) 806 women treated for BC billed out the

same questionnaire as in the previous study. The data showed that among these respondents, physical activity reduced and body weight and BMI increased in the last 3 years. In addition, women who had higher BMI had a lower total score of physical activity at all levels (moderate 28%, intensive 64%, and sports 49%) than women with normal BMI. Yet, during the first year after diagnosis, in the group with BMI < 30 kg/m^2 some increase in physical activity for the moderate and intensive activity was registered. It is interesting that women diagnosed with higher stage of disease (stage II) consumed 15% more time on physical activity than women with *in situ* disease. Among sports and recreational activities, walking was the most common and most popular activity. According to the U.S. Department of Health and Human Services recommendations (Surgeon General's physical activity recommendation) [39] at least 150 minutes of moderate to intensive activity (more than 3 MET) per week is necessary to maintain health. When observing all activities (total activity), this criterion was met by 73% of women. However, when household activities are excluded from the total score, only 32% of women in this study met the criteria of satisfactory level of activity [54].

It has long been observed that BCS often have a problem with weight gain, especially if they receive adjuvant systemic therapy [55]. In a large study, which included 1,116 women with operable breast cancer in stage I-IIIA disease during a 4-year follow-up period, it was shown that 60% of the patients increased body weight compared to the period before the disease diagnosis, 26% had reduction and 14% had no change. Factors that were positively and independently associated with obesity were: the time elapsed from diagnosis, adjuvant chemotherapy, African-American ethnic background, current energy intake and postmenopausal status at the time of study entry. Factors that were negatively and independently associated with obesity were: BMI before diagnosis, age at diagnosis, the level of education and current level of physical activity [56].

Physical activity and risk of relapse of disease and death in breast cancer survivors

One of the first longitudinal studies that confirmed the importance of physical activity in reducing the risk of death which was dose dependent was published in 2005. The study followed women diagnosed with BC during the period 1984–1998. By June, 2002, 2,987 women in stage I-III disease were followed. According to the level of physical activity expressed in MET-hours *per* week, subjects were divided into categories less than 3, 3–8, 9–15 and more than 15 MET-hours per week, while the group with the lowest level of activity was taken as a reference. The median follow-up period was 8 years. It was shown that the risk of death was significantly higher in the group of women not physically active enough (less than 9 MET-hours per week). This relationship was particularly pronounced among women with hormone-sensitive tumors: active women (more than 9 MET-hours *per* week) had a 50% lower risk of death than less active ones. The lowest risk of relapse and death was noticed in the group who had moderate levels of physical activity (9–15 MET-hours *per* week): the 5-year survival for this group was 97%, while for the group which was active less than 3 MET-hours *per* week, it was 93%. Moreover, with the increase in physical activity to some extent, the risk of death (specific for BC and other causes, as well) decreased, regardless of BMI [34].

Somewhat unexpected, the results of this study related to the fact that the risk of fatal outcome in a group of very intensive physical activity (more than 15 MET-hours *per* week) increased again. The authors associate this information with the impact of the disease stage at the time of diagnosis in women's behavior change. It was shown that women, if the diagnosis is worse, are prone to intensive lifestyle changes. In the group with intensive exercise were more women in stage II of the disease, while the group of moderate trainees comprised more women the stage I disease.

These observations are compliant with the results of the Health, Eating, Activity and Lifestyle (HEAL) study, which compiled data on physical activity 3 years after the BC diagnosis. Specifically, it showed that women with a higher stage of the disease at the time of diagnosis, had 15% more physical activity than those in whom ductal carcinoma (DCIS) *in situ* was diagnosed, although this difference was more in the domain of household activities [54]. In the following study, it was confirmed that the level of physical activity after BC diagnosis is more important from the standpoint of survival than the activity before the diagnosis. Women who increased their activity after BC diagnosis by 45% reduced the risk of death [57].

The latest meta-analysis on the effect of physical activity before and after the diagnosis of BC upon the survival and relapse of the disease, included the six major studies, with a total of 12,108 patients enrolled [58]. To enable the comparison of the results, the authors divided the level of physical activity in four categories: low, moderate, moderate to high and very high. The women from the low activity level group (less than 3 MET-hours per week[*]) were the reference group, used as basis for calculation of the results and the reference level for the comparison of the effects of physical activity on the risk of relapse and death. The results of three studies that examined the effects of primarily recreational activities before BC diagnosis on the risk of relapse and death show that physical activity before the diagnosis reduces the risk of death from all causes by 18%, but has no effect on mortality from BC [57, 59, 60]. However, women physically active after the BC diagnosis, compared with physically inactive ones, have 34% lower risk of death from breast cancer, and 41% lower risk of death from all causes. This is shown for all levels of physical activity. Also, moderate and moderate to high levels of physical activity after BC diagnosis reduce the risk of relapse by 24%, but this does not apply to a very high level of activity [58].

Two studies show that obese women (BMI > 25 kg/m^2) with more physical activity after BC diagnosis have a lower risk of death from breast cancer compared to less physically active women [57, 61], but this effect was not registered in

[*] Moderately fast walk (3–5 km/h) for 1 hour corresponds to the activities of 3 MET-hours.

women with normal body weight. On the other hand, more physically active women have a lower risk of death from all causes compared to the less active group, regardless of BMI [57, 62].

Possible mechanisms of influence of physical activity on disease relapse and survival

The mechanisms of physical activity reducing the risk of disease relapse and prolonging survival in BCS are as intriguing as the mechanism of its influence on primary prevention, and, probably, they are similar. The two most frequently mentioned mechanisms are: the impact on steroid hormones (especially on estrogen) [35, 63] and the impact on insulin function [35]. Both of these mechanisms are largely associated with the impact of physical activity on energy balance and body weight.

The importance of energy balance (the ratio between energy intake and expenditure) has long been observed from the standpoint of carcinogenesis and survival [64, 65]. For over 20 years it is well-known that women with increased body weight are exposed to two times higher risk of relapse within 5 years from diagnosis and 60% higher risk of death in the next 10 years, compared to women with normal weight (BMI < 25 kg/m^2) [66]. Central body fat distribution is associated not only with cardiovascular disease but also with some cancers [67–69]. Obesity is associated with the altered metabolism of estrogen [70], and facilitated conversion of androstenedione to estrogen [71, 72], as well as with the increase of insulin resistance, hyperinsulinemia and insulin-like growth factors [73]. According to current knowledge, it appears that exercise changes the pattern of accumulation of adipose tissue, leading to a reduction of abdominal fat [74]. This is especially important for postmenopausal women. After completion of reproductive age, the processes that lead to a reduction in muscle mass and increase in body weight occur more frequently, followed by the change of the distribution of body fat [75].

Sex steroid hormones have powerful mitogen and proliferative effects on breast tissue. Increased levels of circulating estrogen can stimulate the growth of breast cancer [76]. Possible mechanisms for estrogen induced breast cancer include increased breast epithelial cell proliferation, the metabolism of estrogen to genotoxic metabolites, such as DNA-adducts, and the silencing of tumor suppressor genes (TSGs) that have been implicated in breast carcinogenesis by inducing gene promoter hypermethylation, which is potentially reversible [63]. In contrast, lower levels of estrogen and progesterone in the circulation are associated with the reduction of breast epithelial cell proliferation [63, 77]. Because adipose tissue contains a large amount of aromatase, an enzyme that participates in the conversion of androgens into estrogens [72], obese BCS have increased risk of relapse of disease and death [78]. Physical activity can influence the reduction of fatty tissue, thus reducing the capacity of conversion of androgens to estrogens and lowering the levels of estrogen in the circulation [79]. Increased insulin resistance and increased amounts of insulin and insulin-like growth factor (IGF), and a decrease in insulin-like growth factor binding globulin (IGFBG) concentrations are often recorded in obese patients. Anabolic activity of insulin and IGF promote tumor growth by stimulation of cell growth and inhibition of apoptosis *via* the insulin receptor in breast tissue [80]. In addition, these two factors stimulate steroid hormones synthesis in the ovaries and inhibit sex hormone binding globulin (SHBG) production in the liver, which further emphasizes the process of carcinogenesis [81–83].

Acute physical effort improves insulin sensitivity and increases the uptake of glucose from plasma, mainly on the account of the activities of muscle tissue, but this reaction is lost within a few days [84]. However, regular physical activity of moderate or higher intensity maintains insulin sensitivity [84, 85] and protects against the development of insulin-independent diabetes [86]. It is assumed that this is a consequence of reduction in abdominal fat and increase of muscle mass, improved glucose transport in muscles [87] and/or reduced synthesis of fatty acids [84, 85]. In addition, the reduction of plasma insulin levels as a result of physical activity, leads to the production of a larger amount of SHBG which reduces the bioavailability of steroids in tissues, thus reducing the risk of disease relapse [88, 89].

A group of authors from Yale Medical School compared the level of free insulin, IGF-I and IGFBP-3 between the two groups of postmenopausal BCS. The first group had moderate level of regular aerobic activity of their choice for 30 minutes daily 5 times a week during a period of 6 months. The control group did not have specially organized activities, but continued with their normal daily activities. At the end of this period there was a significant difference in the level of IGF-I and IGFBP-3 between the groups. The level of free insulin was lower by 20.7% in the study group compared to the control group, but this difference was not statistically significant. The authors concluded that regular moderate aerobic activity, which was well tolerated by BCS, lowered the levels of IGF-I and IGFBP-3, whose activity was associated with disease relapse [90].

Physical activity – How much?

Previous researches show clearly a negative correlation between physical activity after diagnosis of breast cancer and the risk of disease relapse and death [91]. This correlation is dose- dependent [91] and it is more pronounced for postmenopausal women [62]. Apparently, this ratio is fairly stable, regardless of the level of dietary intake, body mass index, race, tumor stage and histological sub-type [92, 93].

A round table was organized in June, 2009 by the American College of Sports Medicine (ACSM), which brought together eminent experts in the field of rehabilitation of cancer patients, with the aim to search for the evidence of the impact of exercise on various aspects of life of cancer patients and survivors [91]. One of the aims was to provide guidance for treatment of such patients. There was consensus that the recommendations for the level of aerobic physical activity that exist for other chronic conditions are fully applicable to cancer survivors: 150 minutes of moderate to intensive or 75 minutes of very intensive aerobic activity *per* week (or

appropriate combination) [94–96]. In addition, it is recommended to perform exercises that involve large muscle groups, 2 to 3 times a week to strengthen muscles [94, 96]. Flexibility exercises are recommended before any of these two groups of exercises [97]. Of course, the level of physical activity must be adapted to the current state of the patient. According to the latest report of U.S. Department of Health and Human Services (U.S. DHHS) Physical Activity Guidelines for Americans [96], any exercise is better than nothing, and those who are unable to reach the recommended levels of physical activity should still be encouraged to be active as much as they can.

What kind of activities will be selected depends on individual choice, the current state of the body and overall ability of the patient. Walking is still the most popular form of aerobic training, which is entirely satisfactory if performed with the appropriate intensity. According to data from a sample of 2,987 women, intensive, fast walking had a similar effect as other intensive activities such as jogging, tennis or swimming [34].

Conclusion

Physical activity in BCS is particularly useful, not only because it improves physical and psychological health of survivors, but also because it reduces the risk of disease relapse and prolongs survival.

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