

The role of physical activity in the prevention of breast cancer: potential mechanisms of action

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Abstract

Breast cancer is the most prevalent malignancy in women both in Poland and worldwide. It is currently one of the largest epidemiological problems. The health-promoting lifestyle, including physical activity, plays an important role in the primary and secondary prevention of breast cancer. Studies have confirmed the relationship between regular exercise and the risk of developing breast cancer, as well as its course and prognosis. A number of possible mechanisms are involved in linking physical activity with the risk of breast cancer. Nevertheless, they have not been fully elucidated. The most important mechanisms include the impact of physical activity on the immune system, inflammatory processes, sex hormone levels, obesity, metabolic syndrome, and lifestyle. The paper attempts to discuss these mechanisms.

Key words: breast cancer, primary prevention, secondary prevention, physical activity

Introduction

During the 20th century, a considerable lifestyle change was observed. The involvement of muscles during daily activities decreased by 80%, with an increase in the pace of life [1]. Modern women are often characterized by low physical activity, high stress levels, poor nutrition, smoking, alcohol consumption, late motherhood or childlessness. At the same time, these factors are considered significant for the risk of breast cancer. Approximately 95% of all breast cancer cases are associated with lifestyle factors [2, 3].

Breast cancer is the most prevalent malignancy in women both in Poland and worldwide. It is currently one of the largest epidemiological problems. Over 1.5 million new cases are diagnosed annually worldwide, with the highest incidence rate in high-income countries [4]. Poland is among the countries with the average incidence of breast cancer. However, an increasing trend has been recently reported. Over a 2-fold increase in the incidence of this cancer has been observed since the 1990s [5]. In addition, considering the demographic changes in the Polish population and the fact that 80% of all breast cancer patients are diagnosed after 50 years of age, a further increase in the number of cases can be expected [6].

Physical activity is one of the main elements of a healthy lifestyle and plays a crucial role in health promotion. If it is maintained at an appropriate level, it constitutes a preventive measure, reducing the risk of developing diseases of affluence, including cancer [7]. The lack of physical activity is considered a cause of health loss [8]. When physical activity is analysed in the context of cancer diseases, its importance in both primary and secondary prevention should be stressed.

Increased physical activity reduces the risk of breast cancer in active women by 30–40% [9, 10]. In addition, the onset of physical activity and its intensity are also significant, which is in line with most experimental [11–15] and epidemiological studies [16–18].

Regular physical activity in childhood and young age results in a decreased risk of breast cancer in adulthood [19, 20]. This relationship was reported by Frisch et al. [17] as early as in 1985. They demonstrated a significantly lower incidence of breast cancer among former American college athletes compared with non-athletes.

The American Cancer Society developed guidelines for the level of physical activity in cancer prevention. The Society recommended 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity activity each week [21]. Donnelly et al. showed a lower risk of invasive and preinvasive breast cancer in women who were physically active for 5 or more hours per week [22]. Bernstein et al. [23] and McTiernan et al. [24] indicated the intensity level of physical activity. Bernstein et al. [23] indicated that a 20% decrease in the risk of breast cancer was found in active women who undertook 60-minute physical activity with the intensity over 6.7 metabolic equivalents at least once per week for 1 year [23]. In turn, McTiernan et al. [24] noted a 14% decrease in the risk of breast cancer in women who at the age of 35 performed vigorous physical activity 3 times per week.

The benefits of physical activity are also observed in secondary prevention among women who undergo cancer treatment and in those who completed such therapy. A significant improvement in the circulatory and respiratory systems is reported. Additionally, physical activity reduces fatigue and improves the quality of life [25–28]. Women with a high level of physical activity and capacity are also characterized by a 50% lower relative risk of premature death compared with individuals with a sedentary lifestyle [29–31].

Summarizing, physical activity has a multidirectional effect on the human body. A number of possible mechanisms are involved in linking physical activity with the risk of breast cancer. Nevertheless, they have not been fully elucidated [32, 33]. The most important mechanisms include the impact of physical activity on the immune system, inflammatory pro-

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cesses, sex hormone levels, obesity, metabolic syndrome, and lifestyle [34].

Immune system

The activation of immune processes is due to regular physical exercise that increases the activity of the immune system [1]. Physical activity generates the release of cortisol and catecholamines, which results in an increase in the number of some cells of the immune system and changes in the humoral system. The number of natural killer (NK) cells and cytotoxic T lymphocytes can be significantly increased after physical activity (150–300% and 50–100% in the case of NK and T cells, respectively) [35]. Both NK and T cells are the lymphocytes which constitute the first line of defence against pathogens and cells that have undergone malignant transformation. Experimental studies on mice related to breast cancer showed that weakening of the immune system and dissemination of cancer occurred after exogenous oestrogens administration, whereas training on a treadmill for 8 weeks resulted in a reduction in the tumour size, as well as an increase in NK cell and macrophage activity [36–38].

Inflammatory processes

Permanently elevated C-reactive protein (CRP) concentration is an indicator of chronic inflammation. When inflammatory factors are present in the tumour microenvironment, they facilitate the proliferation and migration of cancer cells and angiogenesis. Elevated CRP levels have been shown to increase the risk of lung, kidney, colorectal, and skin cancer in healthy individuals [39]. At diagnosis, elevated CRP in women with breast cancer was associated with decreased overall survival [40]. The Mediterranean diet and physical activity have been proven to reduce the CRP concentration. It was found that concentrations of proinflammatory cytokines, including CRP, tumour necrosis factor- α (TNF- α), and interleukin (IL)-6, were decreased as a result of moderate physical activity [34].

Adiponectin, which was first described in 1995, is one of the many cytokines associated with inflammatory processes. Adipocytes produce adiponectin, whose concentration depends on the amount of adipose tissue. An increase in the concentration of this cytokine occurs when the amount of the tissue decreases. Additionally, adiponectin is responsible for anti-inflammatory and antimetabolic activity, as well as inhibition of angiogenesis and proliferation in breast cancer cell lines [41]. Physical activity indirectly affects high levels of adiponectin. TNF- α and IL-6 regulate gene expression and adiponectin secretion by adipose cells.

Reduction in adipose tissue results in a decrease in TNF- α and IL-6 concentrations, which leads to an increase in adiponectin [42]. Long-term and regular physical activity may cause a decrease in TNF- α and IL-6 concentrations, irrespective of a decrease in adipose tissue. However, this mechanism has not been completely understood.

Regular and moderate physical activity contributes to the normalization of the balance between pro-inflammatory and anti-inflammatory cytokines [34]. Temporary exacerbation of inflammatory processes can be caused by excessive physical activity [33].

Sex hormones

A decrease in the concentrations of sex hormones and an increase in sex hormone binding globulin (SHBG) are the

beneficial effects of physical activity, lowering the risk of breast cancer development [43]. Oestrogens promote cell growth in the breast and also stimulate proliferation [44]. Reduced exposure to oestrogen can be obtained by undertaking physical activity at a young age, which may delay the age of menarche (the later the menarche, the lower the risk of breast cancer) [2, 45]. In premenopausal women, physical activity may reduce the number of ovulation cycles, lowering long-term exposure to endogenous oestrogens and reducing the risk of breast cancer [46–48]. In postmenopausal women, physical activity can affect the levels of endogenous oestrogens by reducing adipose tissue. In obese individuals, fat tissue is a significant source of estrone and oestradiol [48–50]. By reducing the adipose tissue and increasing the level of SHBG, physical activity can also result in a decrease in the testosterone level. However, study results are inconclusive [51].

Obesity and metabolic syndrome

In recent years, overweight has become an important epidemiological problem in high-income countries [52]. Both obesity and metabolic syndrome significantly increase the risk of many different types of malignancies, including colorectal, gallbladder, breast, endometrial, ovarian, prostate, and thyroid cancer. High body mass index considerably affects the development of breast cancer. Studies show a higher risk of breast cancer in obese women compared with those who are slim [53, 54].

It is known that obese women have elevated concentrations of oestrogens that are produced by the ovaries during the reproductive period. However, in the postmenopausal period, they are produced by adipose tissue (an organ of endocrine secretion). A higher risk of carcinogenesis in the breast is reported due to prolonged exposure to oestrogen activity. Metabolic disorders are among the sequelae of abnormal secretion of sex hormones, insulin-like growth factor (IGF), leptin, angiotensin, and adiponectin. These substances are secreted by adipocytes [52]. Rosato et al. [55] indicated that overweight women were more commonly affected by metabolic syndrome, which contributes to breast cancer development, particularly in postmenopausal age.

Of note, regular physical activity can reduce obesity. Hyperinsulinemia reduces SHBG and increases the bioavailability of carcinogenic sex hormones; insulin has mitogenic and synergistic effects with oestrogens in breast cancer cell lines. As a result of physical activity, tissue sensitivity to insulin can be increased, and hence the probability of type 2 diabetes becomes reduced [56]. A meta-analysis demonstrated that women with type 2 diabetes had a 16% higher risk of breast cancer [57]. Physical activity initiates adipose tissue reduction, muscle mass increase, and glucose transport to muscles, which protects against hyperinsulinemia and insulin resistance, associated with a decreased adiponectin concentration and excessive production of IL-6, TNF- α , and leptin [56]. In a study on a group of 50 female mice, it was concluded that training caused changes in IGF-1 and corticosterone, which is a mechanism supporting glucose homeostasis in response to increasing energy expenditure associated with movement [58].

Diet

Physical activity can indirectly influence good health-promoting behaviours, such as a proper diet, reduction or total elimination of alcohol consumption, complete or partial smok-

ing cessation. It is estimated that lifestyle modification can reduce the incidence of breast cancer by 50% [59].

A proper diet based on limiting the caloric content and reducing the amount of fats and cholesterol has a positive effect on a decrease in oestrogens serum concentrations [60]. Products that contain trans fatty acids should be avoided as they contribute to inflammation [61]. Fruit and vegetables are recommended (especially those with a high content of folic acid, antioxidants, and bioactive compounds) in primary and secondary breast cancer prevention. Carotenoids are proven to have a positive impact on reducing the risk of breast cancer [62].

A 1.5-fold higher risk of breast cancer is associated with daily alcohol overuse [63]. Ethanol has a considerable effect on the endocrine system. Ethanol and oestrogens are metabolized by the liver. Excessive alcohol consumption results in hepatocyte damage, which leads to abnormal metabolism of oestrogens, and their elevated concentrations contribute to a carcinogenic effect [64].

Acetaldehyde also influences the development of cancer cells by damaging the DNA and causing the destruction of folates. The deficiency of vitamins and macro- and micro-nutrients in the body increases the risk of developing the disease as a result of excessive alcohol consumption [65].

Limitations

Owing to the heterogeneity of the results in the literature review, it is necessary to conduct further research in the field of both primary and secondary prevention of breast cancer. The mechanisms that would fully explain the correlation between physical activity and breast cancer risk and course have not been fully discovered yet. This article presents only the most important and the most comprehensively studied ones.

Conclusions

Physical activity is considered to be a modifiable risk factor for the development and course of breast cancer. The most important are both the time of taking up physical activity (it is recommended to introduce an active lifestyle from an early age) and its intensity (which should be at least moderate).

The essential mechanisms include the influence of physical activity on the immune system, inflammatory processes, sex hormones concentration, obesity and metabolic syndrome, as well as lifestyle; however, they still need to be discussed in more detail.

Ethical approval

The conducted research is not related to either human or animal use.

Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

The authors state no conflict of interest.

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