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Exercise Training and Prostate Cancer

Saber Saedmocheshi[1*], Marzieh Saghebjo[1], Zakaria Vahabzade[2], Darioush Shikhoelslami Vatani[3]

[1] Faculty of Sport Science, University of Birjand
[2] Faculty of Medical Science, Medicine Department, University of Medical Science Sanandaj
[3] Faculty of Sport Science, University of Kordestan

Corresponding author: physical2012@yahoo.com

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Abstract

Epidemiological studies suggest that environmental factors may mediate the transformation of latent prostate cancer into clinically apparent tumors and that exercise appears to influence this progression. Review of recent systematic reviews, meta-analyses and studies on the topic that have been published in the recent literature. Hypothesized biological mechanisms for the physical activity cancer association include changes in hormone level, reduced percentage of body fat, enhancement of the immune system, and alteration in free radical damage by scavenger systems. The available data indicate that 30-60 minutes per day of moderate-to-vigorous physical activity is needed to be protective against breast and colon cancers. We further identify future directions for research, including a better understanding of the biological mechanisms, the need to standardize physical activity and identify mechanistic end points of physical activity that can then be correlated with outcomes.

1. Introduction

Prostate cancer (PCa) is the most common form of non-cutaneous malignancy and the second leading cause of cancer death affecting men in North America (1). It has been estimated that about one in six men will be diagnosed with PCa during lifetime, and one in 36 will die from the disease (2). The incidence and mortality of PCa varies considerably across countries. This reflects genetic, environmental, and dietary influences. In 2008, there were 903,500 new incidences of PCa worldwide, which accounted for 14% of new cancer cases (3). The age-standardized incidence rate was 37.0 per 100,000, and a 5-fold variation between developing and more developed areas existed, with the developed nations having a much higher incidence (3). Generally, the highest incidences are found in Northern America and Western Europe, and the lowest incidences are in

Eastern Asia, particularly China, Japan and India (4). For instance, in the United States, 186,320 men developed PCa in 2008 (5), with an incidence rate of 85.6 (3). In contrast, in the same year, only 33,802 Chinese men were diagnosed with PCa (6), the incidence rate being 14.5 (3). The differences may be attributed to genetics, diet and lifestyle, as well as differences in health care and under-reporting (4). Screening for PCa using prostate-specific antigen (PSA) testing has become common practice in most developed countries. This has led to a rapid increase in the number of cases being diagnosed with PCa, leading to the increase in the incidence of PCa in Western countries and more recently in the Eastern countries as well (7). The incidence of PCa is expected to continue increasing due to increased longevity and more commonly PSA screening, and therefore it will remain a large and growing health problem.

2. Prostate cancer and risk factors

Although recent research has improved insight into the probable causes and risk factors for PCa, the specific causes still remain obscure. PCa results as a consequence of several different factors. Epidemiology studies have suggested that both genetic and environmental factors may contribute to the initiation and progression of this disease (4, 8). Older men are at a higher risk for PCa, with the incidence increasing with age more rapidly for PCa compared to many other cancers (4). PCa is rarely seen in men below the age of 40, and patients younger than 50 years of age account for less than 0.1% of all men affected with PCa (9). Incidence rate tends to rise fast after age 60 and 75% of PCas are diagnosed in men over the age of 65 (Spickett and Roberston, 2010)(10). Autopsy data suggest that histological cancer also increases with age. Microscopic PCa lesions were found in 15% - 30% in men older than 50 years of age and 60% - 70% in men older than 80 years of age (11). These studies demonstrate that a larger population of men will die with PCa than from PCa (12). Another well-known risk factor for PCa is ethnicity. As depicted by the epidemiology data, the incidence rate of PCa varies greatly across countries and between different ethnic groups (13). The highest rates of PCBs are found in North America, Western and Northern Europe and Australia, with an annual incidence of around 100 new cases per 100,000 of population. The lowest rates are among Asians, specifically men living in China, India and Japan, where the incidence rates are less than 5.8 (6). Although incidence of clinically detected PCa varies, the histological cancer does not follow the trend: the incidence of histological cancer is the same in the United States and Japan (4). More recent report compared PCa prevalence in Japanese population to Russian population, which both has a low penetrance in prostate-specific antigen (PSA) screening. The study found that PCa is found on autopsy in a similar proportion of Russian and Japanese men (14). These data suggest that age is most likely the determinant factor for initiation of PCa and differences of progression to clinical cancer are related to other unknown external factors.

Evidence from migratory studies are in line with this concept. For example, one study found that PCa incidence of Chinese and Japanese men increased noticeably from 1.8 and 5.1 to 14.9 and 16.5 respectively after relocating to North America (15). Genetics is another well-established risk factor for PCa. Studies have shown that risk of developing PCa increases among men with affected relatives (4). Furthermore, the relative risk is positively related with number of affected relatives, degree of relatedness, and negatively related to age of diagnosis of the affected family members (16). For example, men with a first-degree family history of PCa have a two-fold risk compared to others (12). Studies of PCa risk among twin population revealed that concordance rate was higher in monozygotic twins than in dizygotic twins (9, 17), which further confirms that genetics plays a role in PCa development. In addition, a study identified that family history was also a predictor for elevated risk of aggressive PCa (18). As a consequence of unhealthy diet and lack of physical activity, obesity has become a major health problem in western countries. It is estimated that more than one third (35.7%) of the adult population are categorized as being obese in the United States (19). Obesity is linked to multiple chronic medical conditions, such as coronary artery disease, hypertension, diabetes, asthma, and arthritis (20). In addition, obesity has also been linked to the development and progression of several types of cancers, including colon, breast, pancreas and PCa (21). In the United States it was estimated that obesity could account for 14% of all cancer-related death in men, and 20% in women (22). The most common measure of obesity is BMI. According to standards of World Health Organization, a BMI < 25 kg/m^2 is considered normal, 25–29.9 kg/m^2 is overweight and ≥30 kg/m^2 is obese (20). However, BMI is a crude measurement for overall obesity, which does not reflect body fat distribution. Abdominal fat is metabolically more active and also more closely linked to insulin resistance. Waist circumference and waist-to-hip ratio (WHR) are generally used to measure central obesity (23). The epidemiological evidence has inconsistently shown a modest association between obesity and risk of total PCa, and a stronger association may exist for risk of advanced disease (24). Many epidemiological studies demonstrated a positive relationship between obesity and PCa incidence. Another important aspect of lifestyle is exercise. Exercise has been increasingly recognized to play an important role in the primary prevention of various cancers, including PCa (25). Exercise exerts protective effects along the PCa continuum. It has been shown to be associated with decreased risk of PCa. Exercise has also been shown to slow disease progression in patients on active surveillance who are diagnosed with low-grade PCa (26). Furthermore, exercise also reduces comorbidity and improves quality of life (QOL) after treatments for PCa (27). Exercise intervention has a pleiotropic effect, which influences many pathways relating to PCa pathogenesis. Chronic exercise stimulates

endogenous antioxidant protection, reduces systematic inflammation, improves innate immune function and protects from obesity (27). Aerobic exercise also decreases serum levels of several metabolic and sex steroid hormones, including fasting insulin and IGF-I (28, 29). Established scientific evidence shows that regular and vigorous physical exercise prevents some cancers, and can also reduce the incidence of cancer by 30–70% (2). The effect is strongest for breast and colorectal cancer. Evidence of the protective effect on prostate cancer is increasing, although the effect is greatest in more advanced disease and in older men. One study (2) reported reduced prostate cancer incidence by 70% for advanced forms and in older men if performing more than 3 hours of vigorous exercise per week. The protective mechanisms are not well understood, but maintaining normal body weight, controlling stress and anxiety, and maintaining physical fitness all optimize the function of the immune system, which reduces the risk for all cancers If you have been diagnosed with prostate cancer, exercise is an important adjunct therapy to reduce your symptoms, lessen the side effects of radiation and drug therapies, improve your psychological wellness and increase your survival rate. Exercise is particularly important for preventing and managing other, often more life-threatening, chronic diseases, such as cardiovascular disease and type 2 diabetes. These conditions are increasingly recognized as side effects of cancer therapy, particularly AST (2). Additionally, many men with prostate cancer often experience reduced fitness, loss of muscle and bone mass and increased body fat. These effects are partly caused by reduced physical activity, poor nutrition and depression. There is now irrefutable evidence from large prospective studies that regular exercise after cancer diagnosis will actually increase cancer survival rates by 50–60%, with the strongest effect for breast, colorectal and prostate cancers (30). A recent study has reported a 49% reduction in deaths from all causes in patients with prostate cancer who did more than three hours of weekly vigorous activity and 61% lower risk of prostate cancer death (31). Men are generally older when they develop prostate cancer, and so muscle and bone loss and weight (32) gain before diagnosis are common. These factors are considerably exacerbated by AST. Therefore, exercise programs must be prescribed to address specific issues facing the patient. Muscle loss and the associated low strength and power capacity increases the risk of falls, which is a major concern if the patient also has osteoporosis (weak bones). Functional capacity, the ability to perform the tasks of daily living and quality of life are also reduced in these circumstances. An appropriately prescribed exercise program (33) has been demonstrated to increase muscle mass and neuromuscular strength, enhance functional performance and reduce risk factors for metabolic syndrome, cardiovascular disease and type 2 diabetes. These effects, along with improved immune capacity resulting from exercise are the most likely mechanisms for

increased survival rates in patients who remain, or become, sufficiently active (31).

3. Exercise training and prostate cancer

The lack of physical activity and the sedentary lifestyles of the population are responsible for health, social and economic problems. The main aim of the National Institute of Health (NIH) and the American College of Sports Medicine (ACSM) is the promotion of physical exercise in all population groups for the improvement of health and prevention of illness. The long-term objectives are to enhance performance in the undertaking of daily activities and to reduce the risk of pathologies associated with a sedentary lifestyle, such as coronary pathologies, obesity, type 2 diabetes, hypertension, brain hemorrhage and cancer.

The recommendations are similar to those put forward by the American Heart Association and the Centres for Disease Control and Prevention (CDC). There are currently three general perspectives on the relationship between physical exercise and health: rehabilitative, preventative, and a perspective oriented to wellbeing. From the rehabilitative perspective, Alaska found that physical exercise can be considered as an instrument for the recovery of the debilitated or damaged corporal function and the alleviation of its effects on the human organism. Physical activity may be compared to medication and seen as a therapy that is complementary to medical pharmacological treatment for pathologies such as coronary disease, obesity, type 2 diabetes, hypertension, brain hemorrhage and cancer.

4. Exercise and prevention of prostate cancer

Established scientific evidence shows that regular and vigorous physical exercise prevents some cancers, and can also reduce the incidence of cancer by 30–70% (2). The effect is strongest for breast and colorectal cancer. Evidence of the protective effect on prostate cancer is increasing, although the effect is greatest in more advanced disease and in older men. One study (2) reported reduced prostate cancer incidence by 70% for advanced forms and in older men if performing more than 3 hours of vigorous exercise per week. The protective mechanisms are not well understood, but maintaining normal body weight, controlling stress and anxiety, and maintaining physical fitness all optimize the function of the immune system, which reduces the risk for all cancers.

Possible Biological Mechanisms in the Relation

between Physical Activity and Cancer Risk Cancer is a multifactorial disease and various

mechanisms may be operative in cancer inhibition with increased physical activity. These

mechanisms may be dependent on a stage of carcinogenesis, cancer site, type of physical activity, and the individual’s characteristic. Various hypothesized mechanisms for the

protective effect of physical activity against cancer risk have been extensively reported in literature (34-53). The majority of the above-mentioned papers reviewed hypothesized mechanisms contributing to the lowered cancer risk by physical activity, which were actively researched. The main mechanisms include: (a) Increasing gut motility by physical activity; shorted gastrointestinal transit time may protect against colon cancer by decreasing bowel transit time, followed by less opportunity for carcinogens

or cancer promoters contact in the fetal steam and colonic mucosa (40); (b) Influencing levels of prostaglandins; strenuous exercise may increase prostaglandin PGF which acts as an inhibitor of colonic cell proliferation. PGF also increases gut motility. It should be noted that physical activity does not increase levels of prostaglandin PGE2, acting as an enhancer of the rate of colonic cell proliferation; (c) Decreasing levels of insulin and insulin-like growth factors (IGFs), glucose, triglycerides and bile acid secretion or by enhancing the acid metabolism and raising levels of IGF binding proteins (IGFBP-3) and HDL cholesterol (a review of (43)and papers cited therein). IGFs are multifunctional peptides that regulate cell differentiation, proliferation and apoptosis. All those IGFs actions and their binding proteins (54) are important in tumorigenesis (53). High concentrations of circulating IGF-I are associated with an increased risk of lung (55); prostate (56), premenopausal breast (57), and colorectal cancers (58), whereas higher concentrations of IGFBP-3 may be associated with a decreased cancer risks, except for premenopausal breast cancer. Concentrations of IGF-I and IGFBP-3 are dependent on diet and lifestyle factors (38). Dietary

energy restriction may reduce levels of circulating insulin-like growth factors (34). (d) Decreasing time exposure to endogenous sex hormones by delay of menarche, reduction of the number of ovulatory cycles, reduction of ovarian estrogen generation. The study by(٣٧) was the first which showed that the

change in physical activity level from low to moderate is accompanied by the reduction in the serum concentrations of estrogen, estradiol, testosterone, androstenedione and their relatives. Physical activity modifies metabolic hormone levels by lowering concentration of fat produced estrogens, and may also reduce estrogens by increased production of sex hormone binding globulin in both men and women. Increased physical activity may alternate estrogen metabolism. Estrogens, especially estrogen and estradiol exert stimulatory effect on mammary glands (37, 59). The association between body size, physical activity, menopausal status and breast cancer are very complex. Obesity is one of the strongest determinants of increased endogenous sex hormones concentrations in women after menopause and is considered as a very important risk factor for the breast cancer among Logistic regression models are used to obtain maximum like hood estimates of the ORs or to calculate hazards rate ratios (RR) (e.g., Cox

proportional modelling), and associated 95% CI as well as to evaluate the effect of the above mentioned confounding and modifying factors on the relation of physical activity on the breast cancer risk.

Descriptive characteristics of cases and controls are compared using t-tests for continuous variables and chi-square analyses for categorical variables. It is worthwhile mentioning that the accurate measurement of physical activity has been very difficult in epidemiological studies and the techniques used in studies are likely limited by validity and reliability; the correlations between quantitative history survey of physical activity and its direct measure are “rather modest”, however they allow to compare the direction (positive or negative) and magnitude of physical activity influence on cancer development (53, 60). According to recommendations of Powell et al. (1987) the accuracy of physical activity measure may be improved by fulfillment of several criteria (61), among them are: clearly defined categories of physical activity; accuracy of the activity estimation should be examined in respect of reliability and validity of a measure (for example, questionnaire should be tested in a pilot study preceding the case-control study); use of the recall calendar during determination of the lifetime total physical activity (e.g., as in Friedenreich et al. study, 1998 for breast cancer or in the Kriska questionnaire for historical leisure activity, Kriska, 1997); physical activity levels should be calculated for the individual woman; the full range of physical activity types should be determined;

dose of physical activity requires collection of data on frequency, duration and intensity, using responsible and accurate techniques; physical activity should be examined

across a participant’s lifespan. For exhaustive details the reader is referred to the paper of (61) and (40)

5. What type of exercise is recommended?

Do continuous or intermittent aerobic exercise for 20 to 60 minutes per session, three to five times per week at 60–90% of your maximal heart rate (the maximal heart rate is estimated as 220 minus your age in years). Rating of perceived exertion (62) is also a useful method to prescribe the desired intensity of the exercise. RPE for older people should be between 13 and 15 on a 20-point scale, provided you have no other health issues that require a lower intensity. Your total weekly exercise should be 120–150 minutes, depending on the intensity of your aerobic exercise. Resistance (weight) training at an intensity of 6–12 repetitions maximum (RM) performed over 3 sets of 6-8 exercises is recommended for each session with the goal of 2 or more sessions per week. It is important to exercise all the major muscle groups each week and select functional movements such as squat, upright row, shoulder press and other exercises that are similar to tasks of daily living. RM intensity refers to the maximum weight that can be lifted for a given target set. For example, 6RM is the weight that can be lifted only 6 times through the full range of movement and while maintaining correct

technique. Flexibility exercises for major muscle groups involving 2 to 4 sets of each exercise two to three times per week should also be completed. Low bone mineral density and osteoporosis are common in men with prostate cancer, due to their age and particularly if they are undergoing AST. If your bone density is compromised, then it is recommended that impact loading exercise be completed to slow or even reverse your bone loss. However, if you have severe osteoporosis or if your cancer has spread to the bones, a modified program is best for reducing your risk of fractures. An exercise program should not exclude exercises which load the skeleton as this strategy will exacerbate bone loss. Rather, prudent exercise and load selection employed in more controlled environments under the supervision of an Accredited Exercise Physiologist is advised.

Exercise assists in cancer prevention, recovery, and survival. In each of these oncologic settings, patients should be counseled to exercise as vigorously as is safe, and to avoid prolonged sitting. The latter should be emphasized as much as the former, as evidence shows that the harmful effects of prolonged sitting may not be ameliorated by regular exercise. During cancer treatment, exercise should be employed to counter the effects of chemotherapy and radiation, including fatigue and nausea. The current exercise guidelines should be followed, and patients who are able should add some high-intensity exercise to their base of moderate-intensity activity. In the early survivorship setting, exercise should be employed to speed recovery from the effects of surgery and radiation, to return the patient as much as is possible to full function, and to improve the quality of life. Exercise should be continued in late survivorship, to improve overall and cancer-specific survival. Since overall mortality is decreased by exercise, all cancer survivors should aim for a vigorous physical activity program, one that is tailored to their limitations and meets or exceeds the intensities stipulated by current guidelines. Current exercise guidelines for cancer patients recommend a base of prolonged aerobic exercise of low-to-moderate intensity, such as walking, carried out at least 150 minutes per week, in divided sessions. Also recommended is a small amount of resistance training. These guidelines are useful for many patients and should be liberally employed at present. However, the lack of major metabolic benefit for many persons adhering to this moderate-intensity regimen is of concern. For these reasons, exercise regimens that employ high-intensity aerobic activity are now being assessed in the oncology setting. (37, 63) Genetic and epigenetic variations dictate whether a tumor will respond to perturbations in energy balance such as those induced by exercise. Advances in genomics and metabolomics will eventually allow oncologists to predict not only which patients will benefit from exercise, but also what frequencies, durations, intensities, and modalities of exercise will best exploit a particular tumor’s metabolic vulnerabilities.

6. Conclusions

These data suggest biologic plausibility for an inverse relationship between vigorous physical activity and risk of prostate cancer progression, and support the development of clinical trials to examine whether increasing physical activity after diagnosis affects prostate cancer biology and disease prognosis

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