Physical Activity and Cancer Prevention—Mechanisms

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ABSTRACT
WESTERLIND, K. C. Physical Activity and Cancer Prevention—Mechanisms. Med. Sci. Sports Exerc., Vol. 35, No. 11, pp. 1834–1840, 2003. Purpose: This paper presents potential mechanisms by which exercise or physical activity may affect cancer development. Methods: Analysis of published and unpublished experimental and epidemiological data from the cancer-activity literature and from other fields of study are compiled to provide a summary of potential mechanisms by which exercise may mediate cancer development. Results: Exercise appears to have a beneficial effect relative to cancer development, and the reader is referred to other sections of this symposium. To date however, the mechanism(s) remains unknown. Potential mechanisms influenced by exercise include alterations in steroid hormones or insulin/insulin-like growth factors, immune modulation, alterations in free radical generation, changes in body composition or weight, and direct effects on the tumor. Cancer is a complex process. It is clear that multiple mechanisms may be operative and that the characteristics of the individual, type of exercise, as well as type of cancer and stage of carcinogenesis will affect which mechanisms may affect the disease. More experimental research in both animal models and in human clinical studies is needed to understand the basic biological mechanisms underlying the effect of physical activity on cancer. Conclusion: In general, physical activity is associated with reduced risk of cancer development, yet to date, the mechanisms remain unknown. Key Words: STEROID HORMONES, IMMUNE SYSTEM, DNA DAMAGE AND REPAIR, FREE RADICALS, ENERGY BALANCE, INSULIN, OBESITY

How might a physically active lifestyle impact carcinogenesis? To date, the mechanism(s) that underlie cancer inhibition with increased physical activity remain unknown. Several logical biological links between cancer development and exercise exist and have been suggested. These, plus other less frequently mentioned, will be discussed. The purpose of this section of the symposium will not be to answer “How does exercise affect tumor development?” but rather is aimed to stimulate research interest and new investigations in the area of exercise and cancer. The reader is encouraged to think globally—that is, that multiple mechanisms may be operative, that they may vary with individual characteristics (age, gender, menopausal status, race, genetics), with stage of carcinogenesis, type of cancer, and type of exercise or physical activity.

STEROID HORMONES—FEMALES
The sex steroid hormones have powerful mitogenic and proliferative influences and are strongly associated with the development of reproductive cancers in both males and females. The effect of exercise on steroid hormones is frequently cited as a potential mechanism underlying exercise’s effect on cancer development.

Menstrual function. A frequently proposed mechanism for the reduction in breast cancer risk with exercise is the effect of exercise on steroid hormones and menstrual function (41,98). Girls who participate in athletics tend to have a later age of menarche (10,92) and a delay in establishing normal ovarian cyclicity (6). However, it has not been established empirically that exercise causes later age of menarche (53). Self-selection by “late-bloomers” into physically active endeavors is potentially one explanation for the “delay” in menarche. Regardless, early age of menarche is associated with increased breast cancer risk (91). Further, early age of menarche predicts more rapid onset of regular ovulatory cycles during adolescence and higher circulating estrogen levels in reproductive life (5). The number of cycles a woman experiences is also related to risk (91). Later age of menarche and slowed establishment of cycling would decrease the total steroid hormone exposure to the breast (6).

Serum hormone levels. In adult premenopausal women, exercise has been associated with decreased levels of circulating estrogen and progesterone (15), shortened luteal phase (9,55), increased frequency of anovulation (10,14), and an increased incidence of oligomenorrhea and amenorrhea (54). Estrogen and progesterone are powerful mitogens in the breast, and reductions in their circulating levels are associated with decreased proliferative activity (72). The shortened luteal phase that has been observed in response to training (9,55,99) may also result in a decrease...
in proliferation; the luteal phase is reported to be the most proliferative phase of the menstrual cycle in humans (89).

In postmenopausal women, increased physical activity has been found to be associated with decreased serum estradiol, estrone, and androgens (16,65) even after adjusting for body mass index. Increased physical activity has also been associated with increased circulating sex hormone binding globulin (SHBG) concentrations in women (35) resulting in lower amounts of free, active hormone in circulation (25). Although sex steroids may have a less dominant role in postmenopausal woman, the decreased body fat in active individuals (discussed later) would also result in less tissue capable of aromatization of the adrenal androgens to estrogens (86).

**Estrogen selection bias.** Recent data suggest that supplementation with estrogen results in a reduction in physical activity behavior (37). Ovary-intact animals that receive estrogen supplementation perform less voluntary activity than the nonsupplemented animals. There is a dose-dependent response, i.e., increased doses of estrogen result in greater reductions in activity, and this occurs regardless of the age of the animal. These findings raise the question as to whether girls who naturally have lower estrogen levels self-select themselves into sports. Is the relationship observed between breast cancer risk and physical activity simply a function that the active girls have a naturally lower estrogenic environment? This speculation has not been explored.

**Estrogen metabolism.** It may be speculated that more subtle, nonclinically detectable changes may, over the long term, be affecting risk for cancer development. These changes however might not be associated with disturbances in menstrual function or altered fertility. Although not extensively explored, increased physical activity may result in alterations in estrogen metabolism. Estrogens are metabolized primarily through two mutually exclusive pathways via C-2 and C-16α-hydroxylation (101). C-2 hydroxylations results in metabolites without estrogen activity, whereas the 16α-metabolites are relatively potent estrogens (27,94). Increased 2-hydroxylation and/or decreased 16α-hydroxylation has been associated with decreased breast cancer and cervical cancer risk (36,44,83). Interestingly, we have also observed that increased 2-hydroxylation is associated with reductions in prostate cancer risk (64).

Reports have been published indicating increased levels of 2-hydroxylated estrogens in athletes (77,88). Conversely, elevated 16α-hydroxylation has been associated with obesity (81). Data from the laboratory of DeCree and colleagues (21,22) suggest that there are also alterations in methylation of the catechol estrogens (2- and 4-hydroxysterogens) in response to exercise. Methylation of 2-hydroxysterogens yields 2-methoxysterogens, of which 2-methoxyestradiol is powerfully antiangiogenic and is currently in clinical trials for chemotherapy. Although, 4-hydroxylation of estrogen is a more minor player in estrogen metabolism, methylation of the 4-hydroxysterogen would change the genotoxic, reactive 4-hydroxysterogens to inert, 4-methoxysterogens (101).

**Breast development/differentiation.** Breast development is characterized by a period of rapid cell proliferation without terminal differentiation (70), a time in which the breast is more susceptible to carcinogen insult. The first full-term pregnancy induces differentiation of the breast and may change the sensitivity of the breast to both endogenous and exogenous risk factors (78). Animal and epidemiological evidence (18,79) suggests that the window of time between menarche and first full-term pregnancy is critical in establishing breast cancer risk. It is has not been determined whether exercise in young girls differentially affects the development of the breast. In our laboratory, we have observed alterations in cell turnover in the mammary glands of adolescent rats in response to exercise training (95). Proliferation was increased in the first 4 wk of training but was followed by an increase in programmed cell death (apoptosis) in weeks 6 and 8 of exercise. No hyperplasia was evident, suggesting that the increase in proliferation was compensated for by an increase in death. No difference was observed in the number of carcinogen susceptible structures (terminal end buds) in the exercised animals at any time point. Gram et al. (32), in the only study in humans, reported that moderate physical activity, defined as greater than 2 h·wk⁻¹, was inversely associated, albeit weakly, with high risk mammographic patterns after adjusting for parity, menopausal status, and body mass. Active women had less dense breasts and fewer high risk patterns than women who exercised less than 2 h·wk⁻¹ or who were sedentary. Density of the breast is a risk factor for breast cancer (69).

**STEROID HORMONES—MALES**

Chronic endurance exercise in males may affect circulating levels of sex hormones. Both testicular and prostate tumors are responsive to androgens. Some studies have found a depressive effect of exercise (33,97), whereas others have found no effect of endurance training on androgen levels (56). SHBG levels may also be increased, rendering less testosterone available for binding to its receptor (25). Thus, it has been speculated that exercise may decrease cancer risk by altering androgen levels and/or their availability.

There is some evidence, however, that exercise is associated with an increased risk for prostate cancer, particularly in young men (90,93). It has also been observed that there is a positive correlation between upper-body muscle mass and prostate cancer incidence (84), which may be due to increased androgens associated with the greater muscularity (58). Thus, it is plausible that males with genetically predisposed builds for larger muscle mass may selectively choose to participate in athletics and that this explains the increased risk of prostate cancer with increased physical activity. The association between muscle mass, resistance exercise, and prostate cancer risk has not been explored.

In terms of the increased testicular cancer risk in young men and teens (90), the potential mechanism is unknown. Intense aerobic exercise has been shown to result in acute increases in androgens after exercise (34,51). Subsequently,
testosterone levels return to baseline. Patients with testicular carcinoma in situ have been found to have a higher incidence of androgen insensitivity (63). It may be speculated that repeated surges in testosterone, in response to exercise, may somehow detrimentally alter androgen sensitivity, or conceivably, men with a greater predisposition to developing, but who do not have testicular cancer, may be affected more significantly by exercise and hormone modulation. Thus, exercise in those individuals may result in increased risk for cancer. In addition, as mentioned above, greater muscle mass has been positively associated with serum androgen levels (58), and the relationship between exercise and testicular cancer risk may be similar to that for prostate cancer, androgens, and exercise (93).

**IMMUNE SYSTEM**

Excellent reviews have been published on the effects of physical activity on immune function (66,85). Current evidence suggests that the majority of human cancers are nonimmunogenic and, therefore, specific antitumor immune surveillance may not be a major factor. Nevertheless, human cancers are to some degree susceptible to control by innate immune mechanisms. Exercise’s effect on the immune system is frequently suggested as a mediator to cancer development. Modulation of the immune system by exercise has the potential to both inhibit cancer development (through immune enhancement) and promote cancer (through immune suppression). As has been observed for upper respiratory infections (68), too little or too much exercise may increase risk for cancer if the immune system is mechanistically involved in the exercise-cancer relationship.

Exercise and physical training have been shown to affect a variety of innate, immune parameters, both functionally and numerically (13,39). Cytotoxic T lymphocytes, natural killer cells (NK), lymphokine-activated killer cells (LAK), and monocyte/macrophages all play surveillance roles, killing abnormal cells. Regular, moderate exercise appears to enhance proliferation of lymphocytes, increases the number of NK cells and increases LAK activity (66).

In experimental models that have assessed the interaction of exercise, immune parameters, and cancer endpoints, trained mice have higher NK cell activity, resulting in greater clearance of tumor cells and incidence of tumors (57). Additional studies provide evidence of significant elevations in LAK cell activity in physically active mice compared with controls and a trend toward decreased mammary tumors (38). In vivo clearance of radiolabeled tumor cells has also been shown to be enhanced in trained mice compared with sedentary controls (57). Further, experimental enhancement of in vitro macrophage-mediated tumor cytotoxicity has also been demonstrated with training (100) and with single bouts of exercise (20).

Decreased immune function with aging (immune senescence) is an established phenomenon that may account, in part, for the increased risk of cancer with aging (59). The most significant aging-related decrease in immune function occurs in cellular immunity. T-cells decline in number, responsiveness, and proliferation with aging because of involution of the thymus and decreased production of IL-2 (59). Cross-sectional studies have found that elderly men and women who have exercised regularly for several years have significantly improved T-cell function compared with age-matched sedentary controls (59). Thus, it may be speculated that the decrease in cancer mortality and/or incidence seen with greater physical activity is related to an exercise-training attenuation of immune senescence that normally occurs with aging.

**FREE RADICALS/DNA DAMAGE AND REPAIR**

Exercise places the body under oxidative stress and increases the production of oxygen free radicals (43). The increased numbers of reactive oxygen species (ROS) that are generated can potentially result in damage to lipids, protein, and DNA (43). Oxygen free radicals can also cause cell mutagenesis and induction of tumor cell proliferation (24). To counter reactive oxygen species however, the body has an extensive free radical scavenger and antioxidant system (24). In general, the body has adequate antioxidant reserves to cope with ROS production under physiological conditions. However, when ROS production is excessive (such as potentially with prolonged aerobic exercise), an inadequate defense may be overwhelmed by ROS, leading to cell and tissue damage. Reports of increased oxidative damage with strenuous exercise (3,73), yet no changes with moderate exercise (45) have been reported.

There is evidence for exercise-associated increases in antioxidant enzyme repair capacity (superoxide dismutase, glutathione peroxidase, catalase (75)), although there are also reports of increased depletion of antioxidant defenses (42). Thus, it is plausible that exercise could be beneficial or deleterious, depending on the intensity or rigor of the training program, subject characteristics, and nutritional status.

Exercise-associated oxidative damage and repair has the potential to affect all cancers and all ages. Antioxidant repair capacity may be of more significance when a tissue or organ is rapidly proliferating and when repair of critical mutations is most important. DNA-repair mechanisms may be less likely to be able attend to all genetically damaged cells before replication during times when a tissue is rapidly proliferating. For example, development of the breast during puberty is associated with increased proliferation, and it is thought that breast cancer risk is established during this developmental window. Alterations in the amount of oxidative damage or repair capacity in response to exercise during this period of time could have significant long-term impact. Exercise training has also been shown to mitigate the decrease in antioxidant defense that normally occurs with aging (47). Thus, moderate-intensity exercise may be of significant benefit in older populations as a means to slow or stop the loss of antioxidants, which are necessary to deal with the daily production of reactive oxygen species. Severe exercise, however, might overwhelm the antioxidant system potentially leading to damage and increased cell mutagenesis (24).
INSULIN/INSULIN-LIKE GROWTH FACTORS

The role of insulin as a promoter of carcinogenesis in various organs, including colon, liver, pancreas, breast, and endometrium, is receiving increased attention (52,96). Serum insulin levels have been reported to be elevated in individuals with cancer but without other diseases related to hyperinsulinemia (23). Noninsulin-dependent diabetes mellitus (NIDDM) is characterized by an extended period of insulin resistance before appearance of clinical symptoms. If the insulin-promotion hypothesis is correct, individuals with NIDDM would be expected to be at greater risk for cancer development. This has been found to be case for cancers of the colon, liver, pancreas, endometrium, and breast; the prevalence of NIDDM is positively associated with cancer incidence (40,62).

Insulin levels and risk for NIDDM are strongly influenced by physical activity, obesity, and fat distribution (11,61). Exercise training results in increased insulin sensitivity, decreased insulin concentrations, decreases in C-peptide (a marker of insulin production), and increased glucagon (49,74). Exercise also appears to be able to compensate for insulin resistance caused by other factors such as high-fat diets (46).

Hyperinsulinemia produces an increase in circulating insulin-like growth factor-1 (IGF-1) and a decrease in the IGF-binding proteins (increasing the availability of IGF present) (19). IGF-1 is thought to have a major role in promoting carcinogenesis (96). Although exercise has been associated with increased IGF-1 (67,82), there have also been reports of decreased levels with chronic exercise (26,67). IGF-binding proteins have also been shown to be altered in response to exercise (17,67). The effects of exercise on the insulin receptor, insulin-receptor kinase activity, insulin-receptor substrate-1, and its phosphorylation remain to be investigated but are altered in obese subjects (31) and might be expected to be changed in response to exercise.

ENERGY BALANCE/BODY COMPOSITION

The importance of energy balance, that is, energy intake minus energy expenditure, in carcinogenesis has consistently been demonstrated for over half a century (1,28). Calorie restriction is profoundly protective against tumor development (48), and exercise has been viewed as the opposite side of the energy balance coin, i.e., increased energy expenditure = decreased calorie intake. However, in most cases, humans and animals have compensatory mechanisms that result in consuming more food to satisfy energy needs. Further, there are multiple physiological and biochemical changes that occur in response to exercise that do not occur with calorie restriction. Therefore, it is questionable whether one can equate increased energy expenditure with decreased energy intake (calorie restriction).

Obesity is a risk factor for multiple cancers (1). As such, it has been proposed that the putative relationship between physical activity and cancer occurrence could be due to the mutual relationship with obesity. However, studies that have controlled for weight or body mass index have however found that exercise is independently related to cancer risk (2,60,87).

Obesity is associated with altered estrogen metabolism (81), facilitates conversion of estrogens from androstenedione (86), and is associated with insulin resistance, hyperinsulinemia, hypertriglyceridemia, and elevations in the insulin-like growth factors (8). Active people generally are not overweight or obese. Central body fat distribution has also been associated with certain cancers (30,80) and is postulated to be due to insulin resistance and hyperinsulinemia (30,50). Exercise appears to favorably modify this deposition pattern, resulting in a reduction in abdominal fat (71). This may be particularly important with aging as fat distribution changes in women at menopause (7) and weight gain/muscle mass loss is prevalent in both genders with increasing age. In animal models, inhibition of chemically induced mammary cancers has been associated with decreased body fat (12). Gillette et al. (29), however, provided evidence that body fat reductions in exercise-trained rats did not necessarily result in cancer inhibition when compared with the calorie-restricted rats that had higher percentage body fat.

DIRECT EFFECT ON THE TUMOR

Is there a reduction in nutrient availability to the tumor? Is there blood flow redistribution away from the tumor to the active skeletal muscles? Or is there a release of cytotoxic substance from the exercising muscle that directly affects the tumor? We and others have observed that exercise training results in smaller tumors and a reduction in growth rate (76,95). New microarray data (K. Westerlind, unpublished data, 2003) on tumors from exercised and sedentary animals suggest that certain genes associated with proliferation, aggressiveness, and cell survival are decreased in RNA isolated from tumors from exercised animals, whereas a smaller number of genes associated with growth arrest and have increased expression in the “exercised” tumors. The mechanism that underlies tumor growth retardation remains unknown but may have important implications for men and women with cancer or preneoplastic disease.

FUTURE DIRECTIONS

The case for exercise having a beneficial effect relative to cancer development is persuasive although incomplete. The relationship between physical exercise and cancer is complex. Cancer is not simply one disease but many diseases involving both genetic and environmental factors. Evidence for a beneficial effect of exercise will be strengthened with more experimental studies, development of mechanism-driven biological markers to evaluate in human studies, and continued analysis of data sets with improved methodologies for assessing and quantifying physical activity. Better understanding of the physiological, immunologic, and hormonal responses to exercise by sex, age, etc., are crucial to move from establishing association to understanding cause. The amount and type of physical activity required to afford protection is not known for any of the cancer types. The
optimal age to begin exercise is unknown, as is the duration of exercise needed for protection.

There is a need to study the potential for inhibition and stimulation of cancer development with physical activity. What is an optimal dose? Does some level of exercise promote cancer development? Most analyses categorize individuals as active or inactive. Demonstration of a dose response would strengthen inference of a causal relationship and would help define “optimal” dose of exercise.

Future research needs to consider the age of individuals and stage of carcinogenesis. Information on the effects of exercise on a genetically susceptible population should be determined, as should the effects in different ethnic and racial groups. Genetics play a role in susceptibility to cancer. Genetics may also play a role in body build, physical functioning, and capacity for conditioning.

Research needs to be directed at the effects of exercise on prognosis in current cancer patients, on the development of secondary cancers in survivors, and on the process of metastasis. Early detection and more effective surgical and chemotherapeutic treatments have resulted in increased survival rates over the last few decades. Thus, the increased incidence of cancer combined with improved survival rates have resulted in nearly 8 million Americans alive today with a history of cancer (4). What are the effects of physical activity in these populations?

Both animal models and human epidemiological studies suggest that regular, moderate physical activity may reduce risk for developing cancer. There appear to be a wide variety of potential mechanisms. In addition to those described in this section of the symposium, the reader is encouraged to consider other potential mechanistic pathways linking exercise and cancer development. Clearly, there are many questions to be answered concerning who would benefit, when exercise is beneficial, and how much activity is optimal. Nevertheless, it would appear reasonable to suggest that regular moderate physical activity be incorporated into healthy lifestyle for all its already well-established benefits, as well as to potentially reduce cancer risk.

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REFERENCES


