Physical Activity and Cancer

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HIGHLIGHT

"Two of the important avoidable causes of cancer are cigarette smoking and alcohol consumption. If we totally eliminated these two factors, perhaps one-third of all cancers might be avoided. In the search for other modifiable aspects of human behavior that potentially may reduce risk of developing cancer, physical activity emerges as a promising candidate."

INTRODUCTION

Cancer is the second leading cause of death, after heart disease, in the United States today (Boring et al., 1994). In 1994, the American Cancer Society estimated that 540,000 Americans died from cancer, while 1,210,000 new cases of this disease occurred that same year (Boring et al., 1994).

Two of the important avoidable causes of cancer are cigarette smoking and alcohol consumption. If we totally eliminated these two factors, perhaps one-third of all cancers might be avoided (Doll & Peto, 1981). In the search for other modifiable aspects of human behavior that potentially may reduce risk of developing cancer, physical activity emerges as a promising candidate. Higher levels of exercise have been shown to be associated with numerous health benefits, including decreased incidence of coronary heart disease (Berlin & Colditz, 1990), hypertension (Hagberg, 1990), non-insulin-dependent diabetes mellitus (Helmrich et al., 1991) and increased longevity (Paffenbarger et al., 1993). Is there also an association between physical activity and reduced rates of cancer occurrence? This hypothesis—that exercise can reduce cancer risk—is not new; in fact, in the early twentieth century, Cherry (1922) observed that men involved in physically active occupations experienced lower cancer mortality rates than their fellow men engaged in less strenuous jobs.

In this review, we first will discuss potential biologic mechanisms whereby exercise might be expected to reduce cancer risk, then proceed to explore the epidemiologic data on the relation between physical activity and cancer of various sites.

POTENTIAL BIOLOGIC MECHANISMS UNDERLYING AN EXERCISE–CANCER ASSOCIATION

Among the many complex functions of the human immune system is the regulation of susceptibility to cancer. Thus, if exercise can enhance the immune system, it is plausible for physical activity to reduce cancer risk.

As far back as 1902, investigators observed that vigorous exercise (i.e., running a marathon) could influence certain components of the immune system (Larrabee, 1902). Today, investigators have attempted to study the effects of exercise on the immune system in several ways. Markers of immune function examined have included susceptibility to upper respiratory infections and the function of cells (e.g., cells of the monocyte-macrophage system and natural killer or NK cells) that serve as the body's first line of defense against the development and spread of cancer (Mackinnon, 1989; Roitt et al., 1989; Shephard, 1991). Upper respiratory infections have been studied because the human immune system also is responsible for regulating susceptibility to infection.

Available evidence suggests that increasing levels of physical activity, up to a certain point, enhance the immune function; beyond this, immune system function appears instead to decrease (Nieman, 1994; Pedersen & Ullum, 1994; Woods & Davis, 1994). What this cut-point is remains unclear. Moderate amounts of physical activity (e.g., brisk walking) have been shown to reduce risk of upper respiratory infection (Nieman, 1994), as well as enhance the function of cells of the monocyte-macrophage system (Woods & Davis, 1994) and NK cells (Pedersen & Ullum, 1994). At more intense levels of exercise, however, immune suppression appears to occur instead. For example, following marathon-type races, runners appear to have increased rates of upper respiratory tract infections for a one- to two-week period (Nieman, 1994). Also, elite athletes (e.g., cyclists) have increased NK cell activity at rest, but depressed function following intense activity (Pedersen & Ullum, 1994).

To summarize, then, it appears plausible for exercise—at least, in moderate amounts—to reduce cancer risk by enhancing the function of the human immune system.

For site-specific cancers, other mechanisms may operate. With colon cancer, it has long been postulated that a shortened intestinal transit time may reduce cancer incidence by decreasing the amount of contact between potential carcinogens, co-carcinogens or promoters in the fecal stream and colonic mucosa (Burkitt et al., 1971, 1972). Thus, if exercise can reduce transit time within the colon, risk of this cancer may be decreased. However, whether exercise does or does not reduce transit time within the intestine is unclear. Several investigators have shown that exercise does indeed decrease transit time (Holdstock et al., 1970; Cordain et al., 1986; Oettlé, 1991); others have not (Bingham & Cummings, 1989; Lampe et al., 1991; Coenen et al., 1992). Apart from the methodologic limitations of these studies, it is possible that the inconsistent findings resulted because exercise may shorten transit time within certain segments of the gut without affecting total (i.e., oral-anal) transit time (Lupton & Meacher, 1988).

Turning to cancers of the reproductive system, various hormones are necessary for their development. Thus, if exercise can alter the levels of these hormones, this represents another plausible mechanism for physical activity to decrease cancer risk. In females, estrogen, as well as the combination of estrogen and progesterone, stimulate cell proliferation in the breast and so have been implicated in the development of breast cancer (Henderson et al., 1993). Studies of female athletes have shown that training can lower estrogen and progesterone levels (Shangold, 1984). Further, in young girls, strenuous training also can delay the onset of menarche (Warren, 1980), thus reducing a woman's total lifetime exposure to these hormones. In males, testosterone appears to be important in the development of prostate cancer (Gittes, 1991). Strenuous exercise may lower basal testosterone levels, potentially reducing risk of this cancer (Lee et al., 1992).

Finally, exercise may influence cancer risk via its effect on decreasing body weight and reducing body fat. For certain cancers such as colon cancer (Lew & Garfinkel, 1979) and breast cancer (Kelsey & Gammon, 1991), obesity is associated with increased risk.

Physical Activity and Reduced Cancer Risk: Potential Biologic Mechanisms

Cancer Type	Potential Mechanisms
Most cancer types	Enhanced immune system
Colon cancer	Shortened intestinal transit time
	Decreased body fat
Breast cancer	Hormone level changes
	Decreased body fat
Prostate cancer	Hormone level changes

PHYSICAL ACTIVITY AND COLON CANCER

Of the various site-specific cancers, colon cancer has been the most commonly studied cancer. The first detailed epidemiologic study was conducted by Garabrant et al. (1984). They examined the occupation of men, aged 20–64 years, who had developed colon cancer. Based on the estimated amount of physical activity required on the job, men were classified as sedentary, moderately active, or highly active. Investigators also examined occupational data among similarly aged men with cancers other than colon cancer. Using this comparison, investigators reported that sedentary men had 1.6 times the risk of developing colon cancer, when compared with highly active men.

It could be argued that the increased risk observed by Garabrant et al. may have been due to higher consumption of fat in the diet among sedentary men, since dietary fat is associated with increased colon cancer risk (Willett et al., 1990). However, another study by Slattery et al., conducted in Utah, did take into account differences in dietary patterns, as well as differences in body weight (1988). When investigators compared the occupational and leisure-time activities of men and women with colon cancer against the activity patterns of a random sample of the population without this disease, they also found sedentary individuals to be at increased risk. The magnitude of this increased risk was approximately twofold.

In their study of over 17,000 men, followed for up to 26 years, Lee et al. observed that physical activity, assessed at one point in time, did not predict risk of subsequent colon cancer (1991). However, men who were sedentary (expending <1,000 kcal/week) at two time points, separated by 11 to 15 years, had twice the risk of those active (expending >2,500 kcal/week) at both times. This led investigators to postulate that for physical activity to protect against colon cancer, it may be necessary for the activity to be sustained over time. Investigators also put forward an alternate hypothesis: In this study, men were asked, on questionnaires, how much walking and stair climbing they did, the kinds of leisure-time sports and recreational activities they engaged in, and the frequency and time spent on these activities. Investigators then calculated the energy expenditure for each subject, based on these data. Thus, two assessments of physical activity may have increased the precision of activity measurement and allowed investigators to better distinguish between the sedentary and the active men.

To date, 33 publications on the relation between physical activity and colon cancer have resulted (reviewed in Lee, 1994; Markowitz et al., 1992; Vetter et al., 1992; Arbman et al., 1993; Chow et al., 1993; Dosemeci et al., 1993; Fraser & Pearce, 1993; Vineis et al., 1993). The majority—25 publications—have shown that individuals who exercise have a lower incidence of colon cancer than their sedentary counterparts. This relation has been described in the United States, Europe, the Far East, and Australia. The magnitude of increased risk experienced by sedentary persons has been reported to be 1.2 to 3.6 times, with most studies describing the magnitude of increased risk to be between one-and-a-half to twofold. From currently available data, it is unclear whether a gradient relation, i.e., increasing protection with increasing activity, exists (Lee, 1994).

PHYSICAL ACTIVITY AND RECTAL CANCER

Many of the studies of colon cancer above also examined rectal cancer (reviewed in Lee, 1994). In contrast to colon cancer, most studies in which rectal cancer was studied separately (as opposed to those that grouped colorectal cancers into a single category) found no significant relation between increased physical activity and risk of this cancer. Where colorectal cancer was studied as a single entity, investigators tended to report a protective effect of physical activity, perhaps reflecting the relation with colon cancer instead.

PHYSICAL ACTIVITY AND BREAST CANCER

While it is attractive to postulate that exercise can decrease risk of breast cancer as few modifiable risk factors for this cancer exist, available data do not consistently support this hypothesis. Frisch et al. first described an inverse relation between physical activity and breast cancer in 1985. They contacted 5,398 surviving alumnae of the classes of 1925–1981 from 10 colleges or universities by questionnaire and asked them to report whether they had developed breast cancer. These women represented 2,622 former athletes from the institutions and a random sample of nonathletes. A total of 69 breast cancers had developed among these surviving alumnae. When investigators compared the prevalence of breast cancer among athletes with nonathletes, they found that the latter had 1.9 times the risk of the former, after taking into account differences in reproductive characteristics between the two groups.

Subsequent studies did not consistently reproduce these findings (reviewed in Lee, 1994; Pukkala et al., 1993; Zheng et al., 1993; Bernstein et al., 1994; Dorgan et al., 1994). Of eight other publications, three described an inverse relation between physical activity and breast cancer risk; four, no relation; and one, a suggestion of a *direct* association, i.e., risk increased with increasing physical activity.

This last publication used data from the Framingham Heart Study, a study ongoing since 1948 (Dorgan et al., 1994). Subjects in this study are brought in every two years to be examined. In this analysis of physical activity and breast cancer, 2,307 women reported their physical activity to physicians in 1954–1956. They then were followed for the development of breast cancer until 1984. A total of 117 women were diagnosed with breast cancer during follow-up. Investigators divided women into quartiles, based on their level of physical activity. They found that women in the highest quartile of physical activity had 1.6 times the breast cancer risk of those in the least active quartile, and this finding was of borderline statistical significance.

Recently, Bernstein et al. (1994) hypothesized that the timing of physical activity is pertinent with respect to risk for breast cancer. They studied 545 women, aged 40 years or younger, with breast cancer, and compared their physical activity patterns to those of 545 women without breast cancer, who were from the same neighborhood and of the same age, race, and parity. Investigators divided subjects into five categories, depending on the number of hours per week that a woman spent in physical activity, after she had reached menarche. Women who did not spend any time in physical activity had 2.4 times the breast cancer risk of their colleagues who exercised for ≥3.8 hours per week. There was a strong gradient of increasing risk with decreasing hours of physical activity. Investigators did take into account differences in reproductive history, use of oral contraceptives, a family history of breast cancer, and obesity in their analysis. The protective effect of physical activity during young adulthood appeared stronger for women having borne children than for women never having borne children.

PHYSICAL ACTIVITY AND PROSTATE CANCER

As with breast cancer, the epidemiologic data do not consistently support an association between physical activity and risk of this cancer, even though a plausible hypothesis has been put forward to explain the biologic basis for an inverse association (Lee et al., 1992). Of 10 epidemiologic studies on this topic, five observed inverse relations between physical activity and risk of this cancer (reviewed in Lee, 1994). For example, Lee et al. (1992) followed 17,719 men, initially aged 30–79 years, for up to 26 years for the development of prostate cancer. For men aged ≥70 years, those who expended <1,000 kcal/week in walking, climbing stairs, and leisure-time sports and recreational activities had 1.9 times the risk of their more active colleagues who expended >4,000 kcal/week. For younger men, there was no significant association between level of exercise and risk of this cancer.

Another three studies found significant direct associations between level of physical activity and prostate cancer risk. That is, these studies observed risk of this cancer to increase with increasing levels of physical activity. For example, Le Marchand et al. (1991) examined the lifetime occupational physical activity of 452 Hawaiian men with prostate cancer and compared this with the lifetime occupational activity of 899 men without such cancer. Men were classified into five categories of activity, depending on the proportion of their life that they had spent in sedentary jobs or jobs involving only light work. Among men aged ≥70 years, the most sedentary fifth of men had only half the risk of prostate cancer of the least sedentary fifth of men. There also was a gradient relation, with risk decreasing as sedentariness increased. For men aged younger than 70 years old, no clear pattern emerged.

Two other indices of lifetime occupational activity also were created: the proportion of life spent in moderately active jobs and the proportion of life spent in heavy or very heavy work. Neither of these two indices was significantly related to prostate cancer risk. The remaining two studies reported no significant relation between the amount of exercise in men and risk of prostate cancer.

PHYSICAL ACTIVITY AND OTHER SITE-SPECIFIC CANCERS

Because of the potential for physical activity to influence levels of reproductive hormones, investigators have postulated that active individuals may experience lower risks of other reproductive cancers, in addition to breast and prostate cancers. In their study of college alumnae, Frisch et al. (1985) also examined the relation between college athleticism and all reproductive cancers (i.e., cancers of the breast, uterus, cervix, vagina, and ovary). Women who had been nonathletes had 2.5 times the risk of these cancers, compared with women who had been college athletes. In another study conducted in Italy and Switzerland, the most sedentary women, based on self-reported physical activity, had 2.4 to 8.6 times the risk (for physical activity at different ages) of endometrial cancer, compared with the most active women (Levi et al., 1993). However, a study from China did not find risk of cancers of the corpus uteri or ovary to differ between women who were inactive or active on the job (Zheng et al., 1993).

Meanwhile, among men, investigators from the United Kingdom have reported that physical activity is inversely related to risk of testicular cancer in those aged 15–49 years. Men who did not exercise experienced a doubling of risk of this cancer, compared with those who spent ≥15 hours a week in exercise (United Kingdom Testicular Cancer Study Group, 1994). Using a different measure of physical activity, men who spent ≥10 hours a day sitting had 1.7 times the risk of testicular cancer of those who spent only 0–2 hours sitting.

Other site-specific cancers that have been studied in relation to physical activity include lung and pancreatic cancers (reviewed in Lee, 1994). Currently, the data are insufficient to conclude whether any association exists. For the remaining site-specific cancers, the data have been even more sparse (reviewed in Lee, 1994).

PHYSICAL ACTIVITY AND PATIENTS WITH CANCER

There is little information on whether patients who already have developed cancer do or do not benefit from physical activity. In animal experiments, investigators found that among tumor-bearing rats that were allowed to feed freely, those rats allowed to exercise spontaneously experienced delayed onset of appetite loss when compared with nonexercised rats (Daneryd et al., 1990). In addition, exercised animals were found to have reduced tumor weights. In humans, exercise has a mood-elevating effect and, thus, may improve the quality of life of cancer patients. In a study of 24 women with breast cancer, investigators developed a moderate exercise program for each patient and followed women for six months (Peters et al., 1994). After five weeks, but not at six months, satisfaction with life was significantly enhanced when compared with baseline attitude. Investigators postulated that this may have been due to decreased adherence to the exercise protocol between five weeks and six months. Further, at the end of the six months, these women were found to have increased NK cell activity at rest compared with baseline NK cell activity, indicating enhancement of this aspect of the immune system.

SUMMARY

Exercise has been shown to be inversely related to risk of developing a whole host of chronic diseases in humans, including coronary heart disease, hypertension and non-insulin-dependent diabetes mellitus. Since 1985, there has been accumulating epidemiologic data suggesting that exercise also may decrease risk of cancer, in particular colon cancer. However, exercise appears to be unrelated to rectal cancer risk. With regard to other cancers, because physical activity can alter levels of reproductive hormones, investigators have hypothesized that active individuals should experience decreased incidence of breast or prostate cancer. However, the epidemiologic data do not consistently support this hypothesis. Data on other site-specific cancers have been sparse. Finally, preliminary data suggest that exercise also may be beneficial for cancer patients by improving the quality of life and enhancing immune function; while promising, this needs more careful research.

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