Exercise and Physical Health: Cancer and Immune Function

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Cancer is a leading cause of morbidity and mortality in developed countries. In the United States, with a population of about 250 million, the American Cancer Society estimated that 1.21 million new cases of cancer developed in 1994, while 0.54 million people died from this disease that same year (Boring, Squires, Tong, & Montgomery, 1994). In recent years, several epidemiological studies have suggested a link between physical inactivity and increased cancer risk (see Lee, 1994, for a review). Biologically, it appears plausible for higher levels of physical activity to decrease cancer risk, as various studies have shown that moderate exercise can enhance the human immune system. This will be discussed later in the paper.

Additionally, for site-specific cancers, other mechanisms may underlie the inverse association seen with physical activity. With colon cancer, exercise may decrease risk by shortening transit time within the intestine, thereby decreasing contact between potential carcinogens, cocarcinogens, or promoters in the fecal stream (Lee, 1994). For female and male reproductive cancers, reproductive hormones play an important role in their etiology and spread. Several studies have shown that exercise can alter the levels of these hormones, potentially decreasing risks of these reproductive cancers (Lee, 1994).

This paper will first review the epidemiological literature on physical activity and the risk of developing various site-specific cancers. Then the effect of exercise on the human immune system will be discussed. Finally, because the immune system also regulates susceptibility to and recovery from infections, data on the relation between exercise and one kind of infection, upper respiratory tract infection, will be summarized.

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Exercise and the Risk of Developing Cancer in Healthy Persons

Colon Cancer

Colon cancer has been the most commonly investigated site-specific cancer in epidemiological studies of physical activity. To date, 33 publications have investigated the association between physical activity and colon cancer risk (see Lee, 1994, for a review; see also Arnbom, Axelsson, Fredrikssohn, Nilsson, & Sjödahl, 1993; Chow et al., 1993; Dosemeci et al., 1993; Fraser & Pearce, 1993; Markowitz, Morabia, Garibaldi, & Wynder, 1992; Vetter et al., 1992; Vineis, Ciccone, & Magnino, 1993). In 18 studies, investigators measured only occupational physical activity. These studies may be of limited quality for two reasons. First, because leisure-time physical activity was not estimated, occupational activity may not accurately reflect an individual's total activity level, especially with increasing mechanization of jobs today. Thus, the findings from these studies may be biased if people who are in physically demanding jobs are also systematically less likely to be active during their leisure time. Additionally, in women, activities undertaken outside the job (e.g., household chores and childrearing activities) are likely to make a larger contribution to their total energy expenditure. Second, investigators of these studies, for the most part, used existing records to determine the occupation (and, hence, activity on the job) of study participants. Participants were not directly contacted, so information on potential confounders, such as diet, were unavailable.

The findings from these 18 studies of occupational physical activity have been remarkably consistent: 15 of the 18 studies reported significant inverse relationships between occupational physical activity and colon cancer risk. These studies have been conducted in several different countries, including China, Denmark, Japan, New Zealand, Sweden, Switzerland, Turkey, and the United States. The magnitude of increased risk, comparing those most sedentary with those most active, ranged from 1.2- to 3-fold. In the remaining 15 studies,
investigators examined leisure time or total physical activity and colon cancer risk. The data from these studies have been less consistent than the data from studies of occupational physical activity. Ten of 15 studies conducted among men reported significant inverse associations, whereas only 4 of 10 studies conducted among women did so. Studies that observed no relationship between physical activity and risk of developing colon cancer tended to have less precise assessments of leisure time or total physical activity, using collegiate sporting activities or a single question on questionnaires. The resulting misclassification of physical activity may have obscured a true, inverse association with physical activity. Such misclassification may have also accounted for the less consistent findings in women because existing instruments (e.g., questionnaires) used to estimate physical activity have largely been developed for men and thus are less precise in estimating activities such as household chores.

The magnitude of increased risk among those most sedentary during leisure time or when considering total physical activity, compared with those most active, was 1.4- to 3.7-fold. This parallels the magnitude of increased risk seen in studies of occupational physical activity. Available data do not indicate a gradient or dose-response relation.

Dietary factors may potentially confound the association between physical activity and colon cancer risk. However, several studies that did control for diet in their analyses continued to observe a significant inverse association between physical activity and colon cancer risk. Thus, taken as a whole, the previously mentioned studies indicate that the relation between physical inactivity and increased colon cancer risk is likely to be causal.

How much and what kinds of activity may be helpful in preventing colon cancer are unclear. Only one study quantified energy expenditure in a manner easily translated to practical recommendations (Lee, Paffenbarger, & Hsieh, 1991). These data suggest that at least 1,000 kcal/week consistently expended during leisure time is required to reduce colon cancer risk. With respect to whether intensity of exercise is important, few data exist. Slattery, Schumacher, Smith, West, and Abd-Elghany (1988) reported that for men, decreased colon cancer incidence occurred with higher levels of intense exercise, but not nonintense exercise, while the reverse held true for women.

Rectal Cancer

In many of the studies on physical activity and colon cancer risk described earlier, investigators also studied rectal cancer as a separate outcome (see Lee, 1994, for a review; see also Arbman et al., 1993; Dosemeci et al., 1993; Fraser & Pearce, 1993). Of 11 studies that investigated occupational physical activity alone, 7 reported no significant associations with rectal cancer risk, whereas 3 showed significant inverse associations and 1 showed a significant direct association (i.e., increasing risk with increasing activity). This last study may have reflected a chance finding because the finding is at variance with most of the other epidemiological data. In addition, there is no plausible biological basis to explain why risk should increase with increasing physical activity. Of six studies that investigated leisure time or total physical activity and rectal cancer risk, all described no significant association.

Taken as a whole, these data suggest that physical activity and rectal cancer risk are unrelated. Because the rectum is an anatomical continuation of the colon, it may seem somewhat puzzling that physical activity should affect these two sites differently. It is possible, however, that exercise may shorten transit time within the colon without affecting transit time within the rectum because the rectum is only intermittently filled with fecal material prior to evacuation.

Female Reproductive Cancers

Of the female reproductive cancers, breast cancer has been the most common cancer type studied. Nine studies have investigated the association between physical activity and the risk of breast cancer, and one study each investigated the association between physical activity and uterine and ovarian cancer, total female reproductive cancers, and endometrial cancer (see Lee, 1994, for a review; see also Bernstein, Henderson, Hanisch, Sullivan-Halley, & Ross, 1994; Dorgan et al., 1994; Levi, La Vecchia, Negri, & Franceschi, 1993; Pukkala, Poskiparta, Apter, & Viikko, 1993; Zheng et al., 1993). Of the nine breast cancer studies, three measured only occupational physical activity. Two of the studies described significant inverse associations (inactive women having 1.4 times the risk of active women), whereas the remaining study reported no significant association. As discussed previously, studies of women that assess only occupational physical activity are especially prone to misclassification because the energy cost of household chores and tasks traditionally carried out by women is not included. Further, the potential for confounding by reproductive factors exists in these studies because investigators generally did not have access to such data and thus could not control for these factors.

For the remaining six studies that investigated leisure time or total physical activity and breast cancer risk, two observed significant inverse associations (inactive women having 1.9 to 2.4 times the risk of active women), whereas three showed no significant relationships and one reported a direct association (i.e., in-
creased risk with higher levels of physical activity) that was of borderline significance. These data are confusing because the best studies, which did control for potential confounding by reproductive factors, reported findings for breast cancer that were diametrically opposite: Bernstein et al. (1994) observed an inverse relationship with physical activity, but Dorgan et al. (1994) noted a direct relationship. The former study investigated women aged ≤ 40 years, whereas the latter study investigated women aged 35-68 years. A possible explanation for the discrepant findings might be that physical activity is inversely related to breast cancer risk in younger, but not older, women (although the biological basis for this remains unclear). Additionally, the latter study may not have been able to measure physical activity as precisely because investigators assessed physical activity as baseline only and then followed women for breast cancer development over a 28-year period.

For other female reproductive cancers, one study reported that occupational physical activity did not influence risk of uterine or ovarian cancer (Zheng et al., 1993). In another study, investigators found that participation in college athletics was inversely related to risk of all reproductive (breast, uterine, cervical, vaginal, and ovarian) cancers: Nonathletes had more than 2.5 times the risk of these cancers than did former college athletes (Frisch et al., 1985). Finally, one other study examined total physical activity and endometrial cancer incidence, with investigators observing that physical inactivity was associated with a 2.4- to 8.6-fold increase in risk (Levi et al., 1993). In summary, the epidemiological data have been inconsistent; the better-designed studies suggest that physical activity may be inversely related to breast cancer risk. Data on the other female reproductive cancers have been limited.

**Male Reproductive Cancers**

Prostate cancer has been the most commonly investigated male reproductive cancer in epidemiological studies of physical activity. One study examined testicular cancer as the outcome of interest (see Lee, 1994, for a review; see also United Kingdom Testicular Cancer Study Group, 1994).

There have been three studies of occupational physical activity and prostate cancer risk. Two studies described significant, inverse associations (inactive men having 1.2 to 1.5 times the risk of active men) with a gradient of increasing risk with increasing sedentaryness, whereas the remaining study reported an opposite finding for men aged ≥ 70 years—decreasing risk with increasing sedentaryness. Among men aged < 70 years in this last study, physical activity was unrelated to prostate cancer risk. The limitations of measuring only occupational physical activity have been previously discussed.

Of the eight studies of leisure time or total physical activity and risk of male reproductive cancers, seven examined prostate cancer. Three of the seven studies described significant inverse relationships (inactive men having 1.3 to 1.9 times the risk of active men), with one study observing this only among men aged ≥ 70 years, but not among younger men. Two studies reported no significant associations, whereas two others found significantly increased risks of later developing prostate cancer among men who had been athletically active during their college days. The remaining study investigated leisure-time physical activity and risk of developing testicular cancer. Physical inactivity was associated with an almost twofold increase in risk of this cancer. The divergent data from these epidemiological studies do not support a role of physical activity in preventing the development of male reproductive cancers, particularly prostate cancer. However, as with breast cancer, the postulated biological basis for an inverse relationship with exercise is attractive.

**Other Cancers**

There have been few epidemiological studies of physical activity and other site-specific cancers (see Lee, 1994, for a review). The cumulative evidence provides little basis for a strong association between physical activity and risk of developing these cancers.

**Exercise and Patients With Cancer**

There is little information on whether patients who have already developed cancer do or do not benefit from physical activity. Data from animal experiments suggest that spontaneous exercise in tumor-bearing rats may delay the onset of anorexia and reduce tumor weights (Daneryd, Hafrström, & Karlberg, 1990). In humans, exercise has a mood-elevating affect and thus may improve the quality of life of cancer patients (Peters, Löcherich, Niemeier, Schüle, & Uhlenbruck, 1994). The effect of exercise on the immune system of patients with cancer will be discussed later.

**Exercise and the Immune System in Healthy Persons**

The human immune system is a highly complex system, comprising numerous cell types and soluble immune mediators (cytokines) that are produced by various cells of this system. The overall function of the immune system is to rid the body of malignant cells and pathogenic agents. With respect to cancer, the immune
cells primarily responsible for recognizing and killing tumor cells are the natural killer (NK) cells, cytotoxic T lymphocytes, and cells of the monocyte-macrophage system (Roitt, Brostoff, & Male, 1989). To evaluate the influence of exercise on these immune cells, investigators have examined changes either in the number of these cells or in their activity.

Natural killer cells are a subpopulation of lymphocytes that express spontaneous cytotoxic activity against a variety of tumor cells without requiring the involvement of major histocompatibility antigens for recognition of the target tumor cells (Herberman & Ortaldo, 1981). Thus, they represent a first-line defense against developing tumor cells. Natural killer cells are very responsive to exercise; immediately following high-intensity exercise, their circulating numbers increase by 150-300% (Nieman, 1994). In terms of function, investigators consistently have shown that following high-intensity exercise, NK cell cytotoxic activity increases 40-100% before falling 25-35% below preexercise levels by 1 to 2 hr of recovery (Nieman, 1994). Moderate intensity exercise also enhances NK cell cytotoxic activity immediately after exercise; however, subsequent immunodepression does not occur (Pedersen & Ullum, 1994). With regular exercise training, investigators generally have found significantly enhanced resting levels of NK cell activity, both among sedentary people who have undergone an exercise program (Nieman, Nehlsen-Cannarella, & Markoff, 1990), as well as among elite athletes (Pedersen & Ullum, 1994).

The enhancement of NK cell number and activity appears to be mediated by exercise-induced changes in epinephrine, as well as the cytokines interleukin-1, interleukin-6, and tumor necrosis factor-α (Nieman, 1994; Pedersen & Ullum, 1994). Meanwhile, the subsequent down regulation of NK cell activity following high-intensity exercise is likely due to cortisol and prostaglandin release (Pedersen & Ullum, 1994).

Cytotoxic T lymphocytes, like NK cells, function to kill tumor cells. However, unlike NK cells, they require that tumor antigens be presented in association with Class I major histocompatibility antigens (Roitt et al., 1989). High-intensity exercise is associated with increased numbers, in the order of 50-100% increase, of circulating cytotoxic T lymphocytes immediately after the exercise, probably induced by epinephrine (Nieman, 1994). As with NK cells, this increase is transient, and within about 30 min postexercise, the T lymphocytes exit the circulation in large numbers, probably under the influence of cortisol (Nieman, 1994).

The third group of cells important in defending the body against tumor cells is represented by the monocyte-macrophage system. Monocytes are cells that are produced in the bone marrow, stored briefly, and then released into the circulation in transit to tissues or to fixed sites along specialized vessels where they mature into macrophages (Adams & Hamilton, 1984). Macrophages represent another line of defense against malignant cells with their phagocytic, cytotoxic, and intracellular killing capabilities (Roitt et al., 1989). In response to acute exercise, regardless of intensity or duration, the number of monocytes in peripheral blood increases transiently (Woods & Davis, 1994). However, acute moderate or high-intensity exercise does not appear to influence the number of monocytes or macrophages infiltrating the peritoneal cavities of mice provoked by an inflammatory challenge. Instead, high-intensity exercise over several consecutive days may decrease the number of these cells by more than 50% (Woods, Davis, Mayer, Ghaffar, & Pate, 1993). With respect to cell function, moderate exercise enhances the phagocytic activity and cytotoxicity of macrophages (Woods & Davis, 1994). Finally, while it is unclear which immune cells are responsible for exercise-induced production of cytokines that mediate NK cell activity, it is likely that some of these cytokines are secreted by monocytes and macrophages in response to tissue damage that occurs during exercise (Woods & Davis, 1994).

To summarize, the available evidence indicates that moderate exercise can enhance the human immune system. However, it remains unclear what the physiological significance of this might be. That is, although plausible, we do not have direct evidence that it is the exercise-induced enhancement of the immune system which underlies the inverse association between physical activity and cancer risk.

**Exercise and the Immune System in Patients With Cancer**

Little is known about the impact of physical activity on patients who already have cancer and whether exercise can influence metastasis. Data from animal experiments have been inconsistent, in large part due to methodological differences in the experiments (Hoffman-Goetz, 1994). For example, the tumor model used; the animal model chosen; the nature of the animal environment; the timing, duration, and intensity of exercise chosen; and whether exercise is spontaneous or forced all appear to influence findings. In one study of women with breast cancer, investigators reported that after a 7-month program of moderate exercise, patients had increased NK cell activity at rest compared with baseline values (Peters et al., 1994). However, to repeat an issue previously raised, it remains unclear what the physiological significance of this might be. In some animal experiments, investigators have shown that despite exercise-induced enhancement of NK cell activity, the impact of exercise on tumor metastasis may be minimal (Hoffman-Goetz, 1994).

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Exercise and Upper Respiratory Tract Infections

The human immune system also functions to regulate susceptibility to, severity of, and recovery from infection. Thus, because exercise has been shown to affect the immune system, we would expect that exercise can also influence the development of infections. Here the data for upper respiratory tract infections (URTIs) will be reviewed.

Available evidence suggests that people who undertake moderate amounts of exercise have lower risks of URTIs than sedentary persons, but those who engage in high-intensity exercise may be at greater risk (Nieman, 1994). In randomized trials of women, those assigned to moderate exercise (walking 40-45 min per day, 5 days per week) had about half the incidence of URTIs compared with sedentary women in the control group (Nieman, 1994). However, high-endurance exercise, such as marathon running, may increase susceptibility to URTIs. The incidence of URTIs during the 1-2 week period following races of marathon distance or longer was higher among runners than among controls who lived with the runners or those who did not participate in the race. Further, during the 2 months prior to a marathon, the risk of developing URTIs among participants of the race increased with increasing mileage logged per week.

Conclusions and Summary

Over the last decade, there has been accumulating epidemiological data suggesting that exercise may decrease the risk of cancer, particularly colon cancer. However, exercise appears 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. The better conducted studies suggest that exercise may reduce the risk of developing breast cancer. However, the epidemiological data on prostate cancer have been inconsistent. Meanwhile, data on other site-specific cancers have been sparse.

An exciting and emerging body of research has suggested that exercise, at least in moderate amounts, can enhance the human immune system. Theoretically, this provides a further biological basis for expecting an inverse relationship between physical activity and cancer risk. However, the changes seen in immune function tend to be transient in nature; thus, the physiological significance with respect to cancer development is uncertain.

Preliminary data also suggest that exercise may be beneficial for cancer patients by improving the quality of life and enhancing immune function. Although promising, this needs more careful research. Again, it is unclear whether the enhanced immune function is of any clinical significance in retarding the spread of cancer that has already developed. Finally, with regard to URTIs, moderate exercise appears to decrease the risk of this infection, although high-endurance exercise may increase the risk. This finding parallels the changes seen in the immune system in response to exercise and comes as no surprise, as the immune system also regulates susceptibility to infections.

References

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**Author’s Note**

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