ABSTRACT: An informal review of literature on exercise and cancer was undertaken in order to examine the role of exercise in cancer prevention, treatment, rehabilitation, and late survivorship. Population-wide studies show that cancer incidence decreases with increasing physical activity levels. Exercise can decrease the side effects of anticancer therapy, and can aid in recovery and rehabilitation following chemotherapy, radiation, and surgery. Observational studies of breast, colon, and prostate cancer survivors show robust associations between postdiagnosis exercise and decreased cancer-specific mortality. In addition, all-cause mortality in cancer survivors decreases with increasing amounts of exercise. The amount and intensity of exercise required to measure a survival benefit appear to vary by primary tumor type. Decreased breast cancer mortality is seen with the equivalent of 3 hours of walking per week, and decreased colon cancer mortality with 6 hours of walking per week. For these tumors, more vigorous exercise may not improve survival. However, after a prostate cancer diagnosis, more intense exercise is associated with superior survival when compared with walking. The mechanisms behind these differences remain to be elucidated. Further research is also needed to determine the various amounts and intensities of exercise required for optimum cancer prevention, recovery, and survival.

Introduction

“Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it” — Plato (427–347 BC)
activity plays a role in the prevention of many cancers is well known, as is the role of exercise in decreasing treatment side effects, speeding recovery after a cancer diagnosis, and enhancing survival. This article will review these intersections of exercise and oncology, discuss the known mechanisms by which exercise exerts its salutary effects, and touch upon the future directions of exercise research in the oncology setting. Finally, recommendations are provided for clinicians to help patients with and without cancer take advantage of the benefits of physical activity.

Regular Exercise Is Associated With Decreased Cancer Risk

That exercise decreases cancer risk is well known, as many studies document the population-wide inverse association between physical activity and cancer incidence. Epidemiologic data from 73 studies conducted around the world, for example, indicate a 25% reduction in the risk of breast cancer among the most physically active women compared with those who are least active.[1] A recent meta-analysis of 19 studies documents the inverse association between kidney cancer and physical activity.[2] Similarly, numerous studies have established the protective role exercise plays in decreasing the risk of many other cancers, including lung, endometrial, colon, and possibly prostate cancer.[3-6]

Regular Exercise May Not Protect Against Health Risks Associated With Prolonged Daily Sitting

However, the dangers of inactivity are especially problematic among those who are consistently sedentary. The possibility that spending more than 4 hours a day behind a desk or working at a computer increases the risk of many chronic diseases, including cancer, has recently gained attention.[7,8]

The extent of the association between sitting and cancer is not fully known. However, current studies, suggesting that regular exercise may not ameliorate the deleterious effects of prolonged sitting,[9] raise concern. That is, an office worker who exercises daily may still incur an increased risk of cancer simply by sitting for more than 4 hours every day.

A timer can be used to remind persons whose job requires prolonged sitting to rise at least once an hour. Suggested activities include climbing a flight or two of stairs, stretching, calisthenics, or taking a short walk. Some office workers make a habit of taking all phone calls standing up. In addition, if the workplace permits, treadmill desks are available from various manufacturers, or a simple one can be constructed in a home shop. Treadmill desks allow reading, writing, or working on a computer while walking very slowly, typically at the rate of 1 mile per hour.

Physical Activity During Cancer Therapy Decreases Treatment Side Effects

In the middle years of the last century, exercise was not recognized as an important part of cancer treatment. The prevailing notion at the time was that cancer patients undergoing cytotoxic treatments should avoid exertion. However, a 1989 randomized trial of 45 women undergoing adjuvant chemotherapy for stage II breast cancer demonstrated that 10 weeks of interval-based, aerobic exercise not only improved functional capacity and body composition, but it also decreased chemotherapy-induced nausea. This pioneering work demonstrated that aerobic exercise was feasible, safe, and beneficial for patients undergoing chemotherapy.[10-12]

Studies since then have carefully documented the positive effects of exercise on patients undergoing chemotherapy or radiation therapy for many different types of cancer.[13-15] At least one study shows that this decrease in symptom burden extends to elderly patients who exercise while in treatment, including improved self-reported health during and after treatment, less memory loss and shortness of breath during treatment, and less fatigue following completion of treatment.[16]
Exercise has also been shown to ameliorate the sexual dysfunction of men undergoing androgen deprivation therapy for advanced prostate cancer.[17] Fifty-seven men on androgen suppression therapy for prostate cancer were randomized to an exercise group or a sedentary control group. The exercise intervention consisted of supervised aerobic activity and resistance training. After 12 weeks of exercising twice weekly, men in the intervention group reported increased sexual interest and activity. In contrast, sexual interest and activity decreased over the same period among men in the control group.

**High-Intensity Activity Provides More Benefits Than Light Activity**

A recent Cochrane database systematic review of 56 trials encompassing 4,800 subjects found that compared with light exercise, moderate-intensity or vigorous exertion during cancer treatment provided greater improvements in health-related quality of life, physical functioning, anxiety, fatigue, and sleep disturbances.[18]

This suggests that for patients on chemotherapy or radiation, and without contraindications to vigorous exercise, even more benefits will accrue with high-intensity activity. In this Cochrane review, mild exercise was defined as a level of activity that raised the heart rate to 30% to 54% of maximum. Examples of low-intensity activities include walking at a rate of 2 to 3 miles per hour or bicycling at 10 miles per hour. Moderate exercise was defined as activity carried out at 55% to 70% of maximum heart rate. Walking at 3 miles per hour or bicycling at 10 to 20 miles per hour are examples of moderate-intensity activity. Finally, vigorous exercise was defined as that requiring 71% to 95% of maximum heart rate. Running at 5 miles per hour or faster, or bicycling at a speed greater than 20 miles per hour would be considered vigorous activity.

**Exercise in the Early Survivorship Stage**

Exercise plays a major role in the recovery of function following treatment, and in reducing the lingering effects of both the disease and its treatment. A Canadian systematic review and meta-analysis of 14 randomized controlled trials reporting the effects of exercise on 717 breast cancer survivors 35 to 72 years of age showed that exercise consistently increased cardiorespiratory fitness and quality of life, and, less consistently, decreased fatigue.[19]

As in the treatment phase, the optimal type and frequency of exercise that will most enhance recovery in the early-survivorship stage of cancer is unknown. What is becoming clear, however, is that low-intensity exercise typically provides little relief from insulin resistance, adiposity, and excessive inflammation, all of which are considered pertinent to the progression of many common cancers.

In the RESTORE trial, 82 women enrolled within 4 to 12 weeks of surgery for early-stage breast cancer were randomized to exercise plus lymphedema education or to lymphedema education only. The exercise program consisted of 30 minutes of moderate walking, 20 minutes of upper and lower body strength training, and 10 minutes of stretching, all done twice a week for 18 months. Adherence through the 18-month period was 79%. Although a significant improvement in the 6-Minute Walk Test was reported in the exercise group, no benefit was seen in other parameters, such as quality of life.[20]

This study and other studies demonstrate that not all exercise is equally beneficial for cancer survivors, and that physicians still have little to guide them when deciding how to prescribe exercise for a particular patient.

The authors of the Canadian meta-analysis described above note “the wide variability in study interventions,” and conclude that “the diversity in exercise prescription is not surprising, given the lack of consensus on the optimal exercise prescription for this patient population.”[19] In the 14 studies comprising the Canadian review, the exercise modalities ranged from walking to weight lifting, stationary cycling, tai chi, and jogging, highlighting the need for more orderly assessment of exercise modalities in future research.
In addition, optimal timing of exercise in relation to the cancer-survivorship spectrum may be important. For example, in the same Canadian meta-analysis of exercise studies in breast cancer survivors, the two studies demonstrating an improvement in fatigue were conducted in the post-treatment period. The six studies done in the adjuvant setting found no reduction in fatigue with exercise.

To address these issues, studies are underway to determine the effects of various exercise schedules and modalities on metabolism and fitness.[21]

Finally, patients in the early-survivorship stage often have specific rehabilitation needs related to surgery, radiation, chemotherapy, or the cancer itself. Lymph node dissection and/or axillary radiation can lead to lymphedema of the arm in breast cancer survivors, and this may interfere with exercise enjoyment. Life-saving chemotherapy drugs can leave survivors with peripheral neuropathy. The resulting pain and numbness can affect both the ability and the desire to exercise in previously enjoyable ways. Patients who require limb-sparing surgery for sarcoma treatment may require occupational and physical therapy. Referral to a rehabilitation specialist is appropriate for these patients.

**Physical Activity in Advanced Cancer**

Physical activity also has a role in the setting of advanced cancer, where impaired physical function due to disease progression and anticancer treatment is nearly ubiquitous. A University of Pittsburgh systematic review examined 16 studies involving more than 500 subjects with advanced malignancy, and reported that aerobic exercise, rehabilitation regimens, or group exercise improved physical fitness and function, and increased feelings of vitality.[22] As with other patients who require specialized rehabilitation, it is advisable to refer these patients to an exercise specialist experienced in the care of cancer patients.

**TABLE 1**

Impact of Physical Activity on Common Cancers

Among the most interesting advances in the field of exercise and cancer in the last decade are several observational studies showing that colon, breast, and prostate cancer survivors who exercise enjoy reduced cancer-specific mortality, and that patients with different cancer diagnoses may require various amounts and intensities of exercise to obtain maximum benefit (see Table 1). The Cancer and Leukemia Group B (CALGB) 89803 cohort consisted of 832 subjects with stage III colon cancer. These patients were followed prospectively for a median of 9.6 years. Compared with subjects exercising an hour or less per week, those walking at least 6 hours weekly displayed a 49% decreased risk of mortality over the course of the study.[23] The Nurses’ Health Study (NHS) reinforced this finding. Among 573 colon cancer survivors, those who exercised at least 6 hours weekly gained a statistically significant cancer-specific survival advantage over those exercising less than an hour a week.[24] Compare those rather high exercise volumes to the lower volumes needed to produce a similar effect in breast cancer patients: A NHS cohort of 2,987 breast cancer survivors required only 3 hours of moderate exercise weekly to achieve a statistically significant decrease in breast cancer–specific survival.[25]

The NHS breast cancer findings were corroborated by the Women’s Health Initiative (WHI) Study. Of the 4,643 postmenopausal women with breast cancer who were enrolled in the study, those who walked briskly for only 3 hours a week had a significantly lower risk of overall mortality compared with inactive
Contrast these low exercise volumes and intensities with those in a study of 2,705 men diagnosed with nonmetastatic prostate cancer. This study demonstrated that men who walked briskly for 90 minutes or more each week had a decreased risk of all-cause mortality. Disappointingly, however, brisk walking failed to decrease the risk of prostate cancer–specific death. Furthermore, this study found that more intense exercise carried out for 3 or more hours weekly not only decreased overall mortality compared with just brisk walking, but vigorous exercise also decreased the risk of prostate cancer–related deaths by 61%. Besides walking, other moderate-intensity exercise modalities in this study included golf and weight lifting. Among the more vigorous exercise modalities in this study were squash, running, swimming, tennis, and bicycling.

These studies illustrate the intriguing fact that achieving cancer-specific survival improvements may require less exercise for breast cancer patients than for those with colon cancer, and moreover, that exercise of higher intensity and longer duration may be required to decrease prostate cancer–specific mortality.

In a 2011 review article, Davies et al postulate that exercise-related reductions in breast cancer mortality may be mediated by beneficial reductions in insulin levels, that the benefits of exercise after a diagnosis of colorectal cancer may be related to modulation of oxidative damage to DNA, and that exercise along with a low-fat, high-fiber diet may slow progression of disease in early-stage prostate cancer through a decrease in apoptosis and reductions in levels of serum IGF-1. However, the precise mechanisms through which exercise may influence cancer recurrence and mortality have yet to be established.

Thus, the current guidelines calling for 150 minutes of moderate-intensity aerobic exercise weekly, plus two sessions of resistance training (weight lifting), may not provide equal benefit for all cancer patients.

**Current Exercise Guidelines Fail to Decrease Weight or Insulin Resistance**

Walking the recommended 150 minutes per week fails to improve adiposity, insulin resistance, and inflammation. In addition, walking programs fail to retain adherents; counter-intuitively, the cardiology literature shows that short, high-intensity regimens lead patients to continue exercise regimens for at least 2 years.

Supervised exercise programs incorporating small volumes of high-intensity activity, such as repeated short sprints, not only decrease adiposity and improve insulin sensitivity and inflammation but also achieve these results with an hour or less of exercise per week. This may explain why subjects find high-intensity workouts more engaging than walking programs.

**Specific Populations May Benefit More Than Others**

In the NHS breast cancer cohort mentioned above, subjects who enjoyed the greatest decrease in cancer-specific mortality when they began exercising only after diagnosis were overweight or obese, and they had estrogen receptor–positive tumors. This finding suggests a mechanism—amelioration of adiposity, insulin resistance, and inflammation—related to energy-sensing signaling pathways, and it also suggests that exercise interventions can and should be targeted to patients with tumors sensitive to manipulations of energy balance.

**Some Tumors May Be Insensitive to Exercise Interventions**

Animal studies show that an intact mammalian target of rapamycin (mTOR)/Akt system is required for exercise to produce significant changes in gene expression.

Conversely, activating mutations of PI3K and/or loss of PTEN signaling can render tumors resistant to the
decreases in insulin and insulin-like growth factor, mediated by caloric restriction and negative energy balance. It is conceivable that such mutations may also render some tumors resistant to exercise-induced decreases in insulin and IGF. [46]

That different modes and combinations of exercise, as well as different schedules, durations, frequencies, and intensities have complex metabolic effects is becoming more widely recognized. [47] In the future, as research enables better understanding of the genetic and epigenetic properties of each tumor and patient, more precisely targeted exercise prescriptions will become possible.

Summary

Exercise assists in cancer prevention, recovery, and survival (see Table 1). 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. [48,49]

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.

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