

Physical activity in cancer survivors: implications for recurrence and mortality

Review Article

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Abbreviations: Women's Healthy Eating and Living, (WHEL); randomized controlled trial, (RCT); The Health, Eating, Activity, and Lifestyle, (HEAL); left ventricular ejection fraction, (LVEF); tumor necrosis factor, (TNF);

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Summary

Advances in cancer detection and treatments have resulted in improved survival rates for cancer survivors. These advances have created an opportunity to examine the potential role of lifestyle factors in further reducing the risk of recurrence and extending overall survival. The purpose of the present paper is to review the literature on physical exercise and clinical endpoints in cancer survivors. Our review found that there is very limited research on this topic. Evidence from other populations on cancer incidence, cancer-specific mortality, and all-cause mortality, however, suggests that exercise could potentially affect these endpoints in cancer survivors. Moreover, evidence on the effects of exercise on the purported biological mechanisms for the clinical endpoints also suggests that a relationship is plausible. Despite the limited evidence for a role of exercise in cancer survival, however, we still recommend exercise to cancer survivors based on preliminary evidence for a quality of life benefit. We conclude by suggesting some future research directions that will begin to answer the question of whether or not exercise can affect clinical endpoints in cancer survivors.

I. Introduction

The prospects for surviving cancer have improved dramatically over the past several decades due to earlier detection and improved medical treatments. The most recent estimate of the five year relative survival rate across all cancers and all disease stages is 62% (2003). This figure soars to over 90% for some of the most common cancers if they are detected early (e.g., prostate, breast, and colon). The high incidence rates and improved survival rates have resulted in over nine million cancer survivors in the United States. These improved survival rates have generated interest in behavioral strategies that might further reduce the risk of recurrence and early mortality in this population. Physical activity is one lifestyle factor that has been postulated to affect cancer survival. The purpose of the present paper is to review the literature on the possible association between physical activity and clinical endpoints in cancer survivors.

A. Definitions of physical activity, exercise, physical fitness, and cancer survivor

Physical activity is defined as any bodily movement produced by the skeletal muscles that results in a substantial increase in energy expenditure over resting levels (Bouchard and Shephard, 1994). Although the term "substantial" is open to interpretation, it is often operationalized as an intensity of at least moderate (e.g., 50% of maximal exercise capacity). Leisure-time physical activity is defined as physical activity undertaken during discretionary time, with the key element being personal choice (Bouchard and Shephard, 1994). This form of physical activity is often contrasted with occupational and household physical activity. Exercise is defined as a form of leisure-time physical activity that is usually performed on a repeated basis over an extended period of time (exercise training) with the intention of improving fitness, performance, or health (Bouchard and Shephard, 1994). An exercise training prescription usually includes activity mode (e.g., walking, swimming), volume (i.e., frequency,

intensity, and duration), progression, and context (i.e., physical and social environment). Physical fitness is defined as the ability to perform muscular work satisfactorily and commonly includes the components of body composition, cardiorespiratory fitness, muscular fitness, flexibility, and agility/balance. The National Coalition for Cancer Survivorship defines a cancer survivor as any individual diagnosed with cancer, from the time of discovery and for the balance of life.

B. A framework for examining physical activity and clinical cancer endpoints

We have previously proposed a framework on physical activity and cancer control that predominantly focused on quality of life issues with some attention to clinical endpoints (Courneya and Friedenreich, 2001). In the present paper, we modify this framework to focus explicitly on clinical cancer endpoints (Figure 1). The framework depicts the major cancer-related time periods and the key clinical cancer endpoints that physical activity may influence during each time period.

The first clinical endpoint is cancer incidence. This endpoint cannot be changed for cancer survivors but we review it later because it may provide indirect evidence for the potential role of physical activity in cancer recurrence. Physical activity may also influence the stage of disease at diagnosis. Again, however, this clinical endpoint cannot be changed in cancer survivors. Moreover, we do not review this endpoint because there are no studies on this topic. We do mention disease stage, however, because it is

a possible explanation for the association between physical activity and cancer-specific mortality that has been reported in healthy cohorts. We view treatment effectiveness as a possible mechanism by which physical activity may influence clinical endpoints in cancer survivors. We discuss this issue in more detail later in the paper. The three primary clinical endpoints in cancer survivors, therefore, are recurrence (or disease free survival), cancer-specific mortality (or disease progression), and all-cause mortality (or overall survival). All-cause mortality is particularly important because of the growing number of cancer survivors who are dying from causes other than their primary cancer (Louwman et al, 2001).

We begin by reviewing the evidence for a link between physical activity and these three clinical endpoints in cancer survivors. Given the paucity of research in cancer survivors, however, we draw heavily from studies in other populations. We then review research on physical activity and treatment effectiveness and the purported mechanisms for the clinical endpoints such as energy balance, cardiovascular fitness, sex hormones, and peptide hormones. We recognize that some of these mechanisms may be cancer-site specific whereas others may apply to cancer more generally. Lastly, we conclude with a discussion of practical implications and future directions for the emerging field of physical activity in cancer survivors.

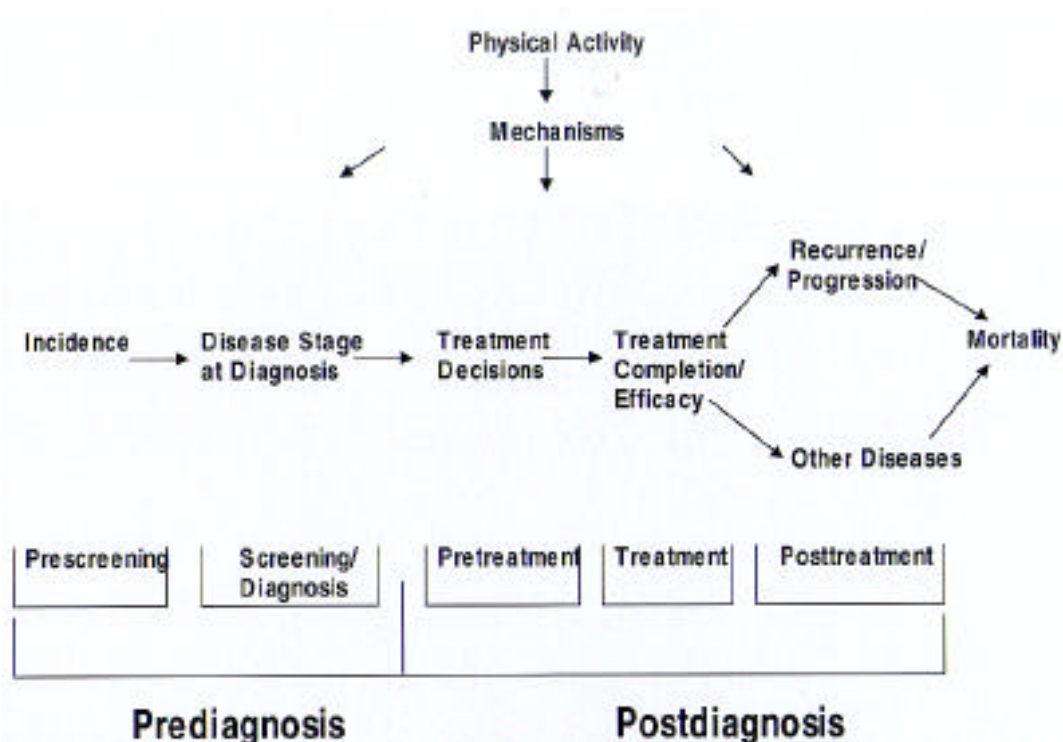


Figure 1. Organizational Framework of Physical Activity and Clinical Endpoints in Cancer Survivors. Adpated with permission of Lawrence Erlbaum Associates from Courneya, K.S. & Friedenreich, C.M. (2001). Framework PEACE: An organizational model for examining physical exercise across the cancer experience. *Annals of Behavioral Medicine*, 23, 263-272.

II. Physical activity and cancer recurrence

No studies have examined the association between physical activity and cancer recurrence in cancer survivors. We are currently following two cancer survivor cohorts for this outcome. One sample consists of over 1,200 breast cancer survivors who participated in one of our case-control studies between 1995 and 1998 (Friedenreich et al, 2001; Friedenreich et al, 2001; Friedenreich et al, 2001; Friedenreich et al, 2002). The second sample consists of almost 1,000 prostate cancer survivors who participated in another of our case-control studies between 1997 and 2000 (Friedenreich et al, in press; Friedenreich et al, in press). Two additional studies that we are aware of are also following cancer survivor cohorts for physical activity and clinical cancer endpoints. The Women's Healthy Eating and Living (WHEL) study is a multisite randomized controlled trial (RCT) examining the effects of a high-vegetable and low-fat diet on cancer recurrence and survival in over 3,000 early-stage invasive breast cancer survivors (Pierce et al, 2002). The Health, Eating, Activity, and Lifestyle (HEAL) study is a prospective cohort study examining the associations between body weight, physical activity, diet, hormone receptor status and prognosis in over 1,000 women with breast cancer (Irwin et al, 2003).

Given the absence of research on physical activity and cancer recurrence, we turn our attention to the cancer incidence literature. Approximately 150 studies have examined the association between physical activity and cancer incidence (Thune and Furberg, 2001; Lee, 2003). The general conclusion from these comprehensive reviews is that there is "convincing" evidence that physical activity reduces the primary risk of breast and colon cancers. The evidence for a link between physical activity and prostate cancer risk is characterized as "probable". The evidence for lung and endometrial cancers is rated as "possible" based on early promising findings. All other cancers are rated as "insufficient" because of the limited number of studies at this time.

It is unclear, however, if research on physical activity and cancer incidence can be extrapolated to cancer recurrence. There are several extenuating circumstances that make us cautious about generalizing the research. First, the biological mechanisms for cancer recurrence may be different than the biological mechanisms for cancer incidence. Second, physical activity may affect the biologic mechanisms differently after a cancer diagnosis because of the effects of the cancer and/or its treatments. Third, the biological mechanisms may no longer be altered by an exercise intervention because of effective standard medical interventions (e.g., antiestrogens). Fourth, exercise may interact with adjuvant therapies in a manner that either potentiates or negates the efficacy of such therapies. Fifth, the older age of most cancer survivors may mitigate against the effects of exercise on the biologic mechanisms because these effects may take years to materialize. Finally, the fact that physical activity did not prevent the primary incidence of cancer in these individuals in the first place (at least for the people who

were exercising prediagnosis) suggests it may not be effective against a possible recurrence.

III. Physical activity and cancer-specific mortality

One study has examined the association between physical activity and cancer-specific mortality in a cancer survivor cohort (Rohan et al, 1995). The study assessed physical activity in 412 breast cancer survivors who had participated in a case-control study. The women were subsequently followed for 5.5 years and 112 breast cancer deaths were documented. The results showed that there was no association between prediagnosis physical activity and breast cancer-specific mortality. There were several important limitations in this study, however, including the assessment of only prediagnosis recreational physical activity over the past year. Logically, it would seem that postdiagnosis physical activity would be most relevant to cancer survival. The breast and prostate studies noted earlier that are examining physical activity and cancer recurrence will also be able to provide data on cancer-specific mortality.

Given the limited data on physical activity and cancer-specific mortality in cancer survivor cohorts, we once again turn our attention to research in other cohorts. To date, 18 studies have examined the association between physical activity and cancer-specific mortality in other cohorts (Polednak, 1976; Garfinkel et al, 1988; Leon and Connett, 1991; Chang-Claude and Frentzel-Beyme, 1993; Wannamethee et al, 1993; Fujita et al, 1995; Kampert et al, 1996; Kushi et al, 1997; Rosengren and Wilhelmsen, 1997; Hakim et al, 1998; Davey Smith et al, 2000; Kristal-Boneh et al, 2000; Batty et al, 2001; Kilander et al, 2001; Rockhill et al, 2001; Farahmand et al, 2003; Gregg et al, 2003; Yu et al, 2003). Of these 18 studies, a statistically significant decreased risk among those most physically active was found in eight studies (Wannamethee et al, 1993; Kampert et al, 1996; Rosengren and Wilhelmsen, 1997; Hakim et al, 1998; Davey Smith et al, 2000; Kilander et al, 2001; Farahmand et al, 2003; Gregg et al, 2003) and a non-significant inverse association was observed in an additional two studies ((Kushi et al, 1997; Rockhill et al, 2001). No association between physical activity and cancer death was found in six studies (Garfinkel and Stellman, 1988; Leon and Connett, 1991; Chang-Claude and Frentzel-Beyme, 1993; Fujita et al, 1995; Batty et al, 2001; Yu et al, 2003) and an increased risk of cancer mortality was found in two studies ((Polednak, 1976; Kristal-Boneh et al, 2000). It is important to note, however, that these last two studies have methodologic limitations that differ markedly from the remaining studies.

The associations between physical activity and cancer mortality are most evident in the studies that examined recreational, rather than occupational activity. No studies to date have examined all types of activity (including occupational, household and recreational activity). Hence, the majority of studies conducted thus far have found either no association or a decreased risk of cancer mortality among the cohort members who were the

most physically active, particularly when the activity examined was recreational.

Generalizing from studies of physical activity and cancer-specific mortality in other cohorts to cancer survivor cohorts is even more problematic than generalizing from studies on cancer incidence to cancer recurrence. In addition to the problems mentioned for the cancer incidence findings, the cancer-specific mortality studies are also confounded by the fact that physical activity is known to reduce the risk of cancer incidence and may also be associated with an earlier stage at diagnosis. Consequently, the lower cancer-specific mortality in highly active individuals from these cohorts may be attributed entirely to a lower incidence of the disease or earlier stage at diagnosis, rather than to a longer survival after the diagnosis.

IV. Physical activity and all-cause mortality

One study has examined the association between physical activity and all-cause mortality in a cancer survivor cohort, however, it was not the primary purpose of the study (Cunningham et al, 1998). The RCT by Cunningham et al. (1998) was originally designed to examine the effects of a psychosocial intervention on survival in a sample of 66 metastatic breast cancer survivors. In an unplanned ancillary analysis the authors found that self-reported regular exercise was the only nonmedical variable to independently predict survival in this sample. Again, the breast and prostate studies noted earlier will be able to examine the association between physical activity and all-cause mortality.

Numerous studies have examined the association between physical activity and all-cause mortality in cohorts without cancer. Lee & Skerret (2001) reviewed 44 observational studies that examined the dose-response association between physical activity and all-cause mortality. They concluded that there is a clear inverse linear dose-response relationship between physical activity and all-cause mortality in both men and women. More specifically, adherence to current public health guidelines was associated with a 20-30% reduction in all-cause mortality (Lee and Skerrett, 2001). Again, the generalizability of these findings to cancer survivor cohorts may be questioned on the grounds noted earlier.

V. Physical activity and potential biological mechanisms of clinical cancer endpoints

Physical activity may influence cancer recurrence, cancer-specific mortality, and all-cause mortality in cancer survivors through several plausible biological mechanisms. We acknowledge that these mechanisms may overlap and/or be interrelated in a complex causal pathway. Our purpose here, however, is not to discuss how these mechanisms may be interrelated but rather to simply outline the biological plausibility of how exercise may influence clinical cancer endpoints.

A. Treatment effectiveness

Exercise could affect cancer recurrence and mortality through modulation of treatment effectiveness. The key factors may include: (a) treatment decisions; both by the physician and the patient, (b) treatment completion; in terms of discontinuation, dose reductions, or treatment delays (i.e., dose density), and (c) treatment efficacy; based on exercise-treatment interactions.

1. Treatment decisions

Treatment decisions are influenced by the general health and performance status of the survivor. Poor functional status may increase the risk of morbidity and mortality from treatments and may also reduce the chances of successful rehabilitation after treatments. For example, the mortality rate from lung resection surgery is reported to range from 7-11% (Datta and Lahiri, 2003). Maximal oxygen consumption (VO_{2max}) can generally stratify the risk for perioperative complications. Patients with preoperative $VO_{2max} > 20$ mL/kg/min are not at increased risk of complications or death. $VO_{2max} < 15$ mL/kg/min indicates an increased risk of perioperative complications and patients with $VO_{2max} < 10$ mL/kg/min have a very high risk for postoperative complications (Beckles et al, 2003). As a second example, decreased left ventricular ejection fraction (LVEF) is a relative contraindication for the use of potentially cardiotoxic chemotherapy (Peng et al, 1997). A resting LVEF of 50% is usually used as the lower limit of normal values, and may change chemotherapy protocol (Peng et al, 1997).

No studies to date have examined the effects of exercise training on VO_{2max} and LVEF in cancer survivors pretreatment. However, in a RCT in patients with stable chronic heart failure, a supervised exercise training program elicited an increase in ejection fraction in the training group by 16% and an increase in peak oxygen uptake of 2.1 mL/kg/min (Giannuzzi et al, 2003). These results may be of clinical importance for cancer survivors awaiting treatment decisions regarding potentially cardiotoxic chemotherapies or surgical resections. If clinical indices such as LVEF or VO_{2max} are slightly below or near normal cut-off range, an exercise training intervention may be implemented to improve function and allow for potentially lifesaving medical treatments to go forward.

2. Treatment completion

Substantial proportions of survivors have reductions or delays in the dosage of chemotherapeutic drugs. Perhaps as many as 30% of survivors have a reduction of the planned dosage to less than 85% (Fraschi, 2002). Such reductions are believed to effect clinical endpoints (Wood et al, 1994). There are many factors that influence a cancer survivor's ability and/or willingness to complete treatments including the severity of the physical side effects, fatigue, and depression (DiMatteo et al, 2000; Hershman et al, 2003). To the extent that exercise is related to these factors, completion rates may be affected.

To date, however, there are no studies examining the association between exercise and treatment completion rates.

3. Treatment efficacy

Anticancer therapies have multiple mechanisms of action including the generation of free radicals, intercalation between DNA base pairs, and inhibition of topoisomerases. The ultimate effect of these therapies is to induce cellular death via apoptosis. Exercise may potentially activate and/or inhibit a multitude of biologic mechanisms that are important modulators of certain antineoplastic therapies such as the generation of reactive oxygen species and changes in peripheral blood flow. To date, however, there is no research on exercise-cancer treatment interactions. Nevertheless, interactions between exercise and cancer therapies are biologically plausible. Research in pharmacokinetics has shown that exercise can influence drug distribution, absorption, metabolism, and clearance (Persky et al, 2003).

B. Energy balance

Epidemiological data suggest that overweight and obesity at diagnosis, and weight gain after diagnosis, are independent predictors of clinical endpoints in cancer survivors (Chlebowski et al, 2002). A recent review found statistically significant associations between overweight or obesity at diagnosis (body weight, BMI) and increased risk of recurrence or decreased survival in early stage breast cancer survivors in 26 of 34 studies (Chlebowski et al, 2002). Statistically significant associations between body weight gain after diagnosis and increased risk of recurrence or decreased survival were reported in 3 of 4 studies (Chlebowski et al, 2002).

Few studies have examined the effect of exercise on overweight, obesity, and body weight gain in cancer survivors (Courneya, 2003). There is, however, preliminary evidence of the efficacy of exercise as a method of body weight reduction in breast cancer survivors. Segal et al, (2001) randomized 121 early stage breast cancer survivors to supervised exercise, self-directed exercise, or control. Secondary stratified analysis showed that body weight was reduced by 3.8 kg in a subset of women who did not receive chemotherapy in the supervised exercise group. Other data suggest that exercise may reduce body weight (Schwartz, 1999), prevent body weight gain (Schwartz, 2000), and improve body composition (Winningham et al, 1989; Courneya et al, 2003) in breast cancer survivors.

Cachexia is one of the most frequent side effects of malignancy, with up to 50% losing some weight and one-third losing more than 5% of their original body weight. Moreover, cachexia accounts for approximately 20% of cancer deaths (Tisdale, 2002). Although anorexia-driven malnutrition seems to be at the core of the syndrome, the pathophysiology is complex and involves abnormalities in nutrient and energy metabolism resulting in the loss of skeletal and adipose tissue (Sutton et al, 2003). Overall, nutritional interventions have had limited efficacy in this setting (Vigano et al, 1994) and several researchers have

acknowledged that a multimodal intervention combining physical exercise to stimulate protein synthesis with nutritional strategies that provide the necessary amino acids may be an effective therapy (Ardies, 2002; MacDonald et al, 2003). To date, no studies have examined the efficacy of exercise training in the treatment of cachexia in cancer survivors. In animal studies, exercised rats bearing transplanted tumors experienced a delayed development of cachexia (Deuster et al, 1985; Baracos, 1989). Exercise training in other clinical populations (e.g., persons diagnosed with sarcopenia, chronic renal insufficiency, rheumatoid arthritis, osteoarthritis, and HIV/AIDS) has also been shown to mitigate muscle wasting (Zinna and Yarasheski, 2003).

C. Physical fitness

Over the past two decades exercise capacity has become a well established predictor of cardiovascular and overall mortality in healthy and clinical populations. For example, Blair and colleagues (Blair et al, 1989) found age-adjusted all-cause mortality rates declined significantly across increasing physical fitness quintiles in both men and women after statistical adjustment for additional known risk factors of survival (e.g., age, smoking status, cholesterol level, systolic blood pressure, fasting blood glucose level, etc.). Further investigations have confirmed these observations (Blair et al, 1995; Lee et al, 1999). More recently, Myers et al, (2002) examined mortality rates in over 6,000 men referred for treadmill exercise testing. After adjustment for age, exercise capacity was the strongest predictor of risk of death among both normal subjects and those with cardiovascular disease. Moreover, in several subanalyses it was shown that this association held for persons with diabetes, high blood pressure, high cholesterol, chronic obstructive pulmonary disease, and for persons who were smokers and obese. No subanalysis was performed for cancer survivors. Lastly, Gulati and associates replicated Myers's findings in over 5,000 asymptomatic women and found that exercise capacity is an independent predictor of death (Gulati et al, 2003).

Two studies have found a significant inverse association between physical fitness and cancer-specific mortality (Lee and Blair, 2002; Sawada et al, 2003). These two studies measured cardiorespiratory fitness in cohorts of Japanese men (Sawada et al, 2003) and men participating in the Aerobics Center Longitudinal Study (Lee and Blair, 2002). Follow-up for cancer deaths was on average 10 years in the United States cohort and 16 years in the Japanese cohort. In the Japanese cohort, men whose physical fitness was in the highest quartile as compared to those in the lowest quartile experienced a nearly 60% reduction in risk of cancer death. The risk reductions were not as strong in the American cohort, nonetheless, men who had moderate versus low fitness had a risk decrease of 38%. Hence, from these two studies, there is some evidence that having high physical fitness decreases the risk of cancer-specific mortality in males.

Exercise has been shown to improve physical fitness in cancer survivors. An early RCT of breast cancer

survivors receiving chemotherapy (MacVicar et al, 1989) showed that a 10 week exercise training program improved VO_2max by 40% compared to the control group. A similar study of hospitalized bone marrow transplant survivors showed that exercise maintained fitness levels while the control group had a 27% decline in fitness (Dimeo et al, 1997). As a third example, Courneya et al. (2003) showed that 15 weeks of exercise training in breast cancer survivors who had recently completed treatment resulted in a 17.7-% change in physical fitness in favor of the exercise group.

D. Mechanical

Bowel transit time is a primary explanation for the association of physical activity and primary colon cancer risk. A decreased bowel transit time would reduce carcinogen exposure time at the mucosa, lowering the risk of initiation or promotion of carcinogenesis by fecal carcinogens (McTiernan et al, 1998). Liu et al, (1993) examined the effect of two weeks of reduced activity on gastrointestinal transit time in healthy elderly subjects who had engaged in regular exercise for 10 years. The mean colonic transit time almost doubled from 10.9 ± 2.7 hours to 19.5 ± 2.9 hours during physical inactivity periods. Similarly, Koffler et al, (1992) gave elderly men a 13-week total body strength training program to examine its effect on gastrointestinal transit time. The training significantly accelerated whole bowel transit time relative to pretraining values from 41 ± 11 hours to 20 ± 7 hours.

E. Quality of life

Quality of life at diagnosis appears to predict cancer survival although studies have focused primarily on cancer survivors with advanced disease (e.g., lung, breast). For example, Herndon et al, (1999) studied 206 cancer survivors with non-small cell lung cancer in a clinical trial. Survival was predicted by baseline scores of a quality-of-life instrument for pain, appetite loss, fatigue, lung cancer symptoms, physical functioning and overall quality of life. When clinical factors such as histology, weight loss, dyspnea, and other factors were taken into account, however, only one score from the quality of life instrument was still predictive, self-rated pain. In a cohort of 181 cancer survivors with advanced disease, self-rated health was observed to be the strongest predictor of survival from baseline (Shadbolt et al, 2002). The relative risk (RR) of dying was 3 times greater for fair ratings compared with consistent good or better ratings at 18 weeks (Shadbolt et al, 2002). Further, Wisloff and Hjorth, (1997) assessed the prognostic significance of quality of life scores and found a highly significant association with survival from the beginning of therapy for physical functioning as well as role and cognitive functioning, global quality of life, fatigue and pain.

Exercise has been shown to enhance quality of life in cancer survivors with early stage disease (Courneya, 2003). For example, Courneya et al. (Courneya et al, 2003) examined a 15 week exercise intervention in breast cancer survivors who had recently completed treatment. They reported a statistically significant and clinically

meaningful change of almost 9 points in quality of life favoring the exercise group. Segal et al. (Segal et al, 2003) examined a 12 week resistance training program in prostate cancer survivors receiving androgen deprivation therapy and also found statistically significant and clinically meaningful changes in quality of life favoring the exercise group.

F. Immune function

Recent data suggest that immune function may be important in the clinical outcome of cancer survivors (Sephton et al, 2000; Demaria et al, 2001; Kay et al, 2001; Lowdell et al, 2002; Liljefors et al, 2003; Zhang et al, 2003). For example, Sephton et al. found that blood levels of CD3-CD56+ cells were positively associated with survival in metastatic breast cancer survivors (Sephton et al, 2000). Liljefors et al. (2003) found that pre-treatment natural killer cell cytotoxic activity was positively associated with progression-free and overall survival in colorectal carcinoma survivors. Kay et al. (2001) showed that blood levels of CD3+, CD4+, CD8+, and CD19+ cells were positively associated with overall survival in multiple myeloma patients. Lastly, Zhang et al. (2003) showed that the presence of CD3+ tumor-infiltrating T cells was positively associated with progression-free and overall survival in advanced ovarian carcinoma.

A recent systematic review found preliminary evidence that exercise can improve immune function in cancer survivors (Fairey et al, 2002). The improvements that have been shown include increased natural killer cell cytotoxic activity, monocyte function, and the proportion of circulating granulocytes (Fairey et al, 2002). However, several methodological limitations of this research were identified including nonrandomized experimental designs, heterogeneous samples, and inappropriate statistical analyses (Fairey et al, 2002).

G. Peptide hormones

Insulin, insulin-like growth factors, and insulin-like growth factor binding proteins have been implicated in clinical endpoints in cancer survivors (Yu and Rohan, 2000). For example, Goodwin et al, (2002) showed that high fasting insulin levels were associated with distant recurrence and death in breast cancer survivors. Although the data are not consistent, several investigators have shown that high levels of IGF-I and/or low levels of IGFBP-3 have been associated with an increased risk of breast cancer and adverse prognostic factors (Yu and Rohan, 2000).

One study has examined the effects of exercise training on peptide hormones in cancer survivors. In an RCT, Fairey et al, (2003) found that exercise training had no significant physiologic effects on fasting insulin, glucose, insulin resistance, IGF-II, or IGFBP-1 in postmenopausal breast cancer survivors. These results are in contrast to previous observations in healthy older adults (Ross et al, 2000; Boule et al, 2001; Duncan et al, 2003). The investigators did find, however, that exercise training had significant physiological effects on IGF-I, IGFBP-3, and IGF-I:IGFBP-3 molar ratio. Other trials of exercise training and IGF-I and IGFBP-3 in healthy older adults

have reported mixed results on these endpoints (Poehlman et al, 1994; Kohrt et al, 1995; Vitiello et al, 1997; Maddalozzo and Snow, 2000; Parkhouse et al, 2000; Hakkinen et al, 2001; Lange et al, 2001; Borst et al, 2002; Schmitz et al, 2002), making it difficult to draw definitive conclusions.

H. Sex steroid hormones

The sex steroids-estrogen, progesterone, and androgens-regulate reproductive function, and have been linked to the development and progression of breast, ovarian, endometrial, and prostate cancer (Persson, 2000; Taplin and Ho, 2001; Modugno, 2003). For example, estrogen has been linked to primary breast etiology and recurrence (Clemons and Goss, 2001). A review of RCTs found that ovarian ablation to eliminate estrogen production results in a significant decrease in breast cancer recurrence and death (Group, 1996).

The contribution of estrogen to recurrence has led to attempts to block the activity of estrogen with pharmacologic agents such as tamoxifen. A meta-analysis confirmed that 5 years of adjuvant tamoxifen in women with node-positive disease improved 10 year survival by 11% (Group, 1998). In postmenopausal women, estrogen depletion with anastrozole (Baum et al, 2003) or letrozole (Goss et al, 2003) further reduces the risk of recurrence. Similarly, androgen deprivation is the mainstay of prostate cancer treatment (Hellerstedt and Pienta, 2003) and induces remission in 80-90% of advanced cases.

To date, there is limited literature on the effect of exercise on sex steroid hormones in cancer survivors. The only study to report on this issue found that 12 weeks of resistance training in prostate cancer survivors on androgen deprivation therapy did not change resting testosterone levels (Segal et al, 2003), which is not surprising given the nature of the treatment. Comprehensive reviews by DeCree (De Cree, 1998) and Consitt (Consitt et al, 2002) outline the effects of exercise on female sex steroid hormones in premenopausal women without cancer. Short-term increases in estrogen levels is seen with acute aerobic exercise, and appears to be dependent on intensity of the exercise and phase of the menstrual cycle (Consitt et al, 2002). Moreover, chronic aerobic exercise in normally cyclic premenopausal women lowers resting levels of estrogen, progesterone, and testosterone, and increases levels of SHBG (De Cree, 1998; Consitt et al, 2002).

A review by Hackney, (1996) outlines the effects of aerobic exercise training in men. Acute bouts of exercise cause an increase in testosterone levels, proportional to the intensity of the activity, while prolonged submaximal aerobic activity shows an initial increase in testosterone concentration, which then declines as the activity is continued. Reductions of 25% to 50% are typical if the activity lasts two hours or longer. The effects of chronic aerobic training have mainly been studied in runners, who show lower free and total testosterone concentrations at rest (15-30%) compared to aged matched, untrained men (Hackney, 1996). Prospective studies that have attempted to induce hormonal changes with an activity intervention have shown mixed results.

The effects of resistance training on male testosterone levels is reviewed by Kraemer (Kraemer, 1988). Overall, increased serum testosterone is seen with acute resistance training. However, it seems that a threshold exists, and that the resistance activity must be of sufficient intensity, volume, and muscle mass recruitment to cause a change. Chronic resistance training has not been shown to alter resting testosterone concentrations (Kraemer, 1988).

I. Cardiovascular risk factors

Cardiovascular risk factors include traditional factors such as blood cholesterol and blood pressure and non-traditional or novel factors may include pro-inflammatory cytokines such as CRP and interleukin 1 and 6. There are no data, however, that have shown these risk factors to predict cardiovascular disease in cancer survivors. There are also no studies that have examined the effects of exercise on cardiovascular risk factors in cancer survivors. A recent comprehensive review of 51 studies examining the effects of exercise training on blood lipid/cholesterol levels in other populations showed that exercise training increased HDL-C by 4.6% and reduced total cholesterol, LDL-C and TG by 1%, 5% and 3.7%, respectively in adult men and women (Leon and Sanchez, 2001). Moreover, in a meta-analysis of RCTs, Whelton and associates (2002) found that exercise reduced systolic and diastolic blood pressure by 3.8 mm Hg and 2.6 mm Hg, respectively. These reductions were observed for all frequencies and intensities of aerobic exercise in both hypertensive and normotensive participants and overweight and normal-weight individuals (Whelton et al, 2002). Lastly, observational studies from other populations have generally found that more frequent physical activity is independently associated with lower odds of having an elevated C-reactive protein (Abramson and Vaccarino, 2002).

Proinflammatory cytokines appear to have a significant role in cancer-associated wasting. Cachexia appears to be associated with elevated levels of interleukin-1-, interleukin-6, tumor necrosis factor (TNF), C-reactive protein and interferon- (Tisdale, 2002). Acute exercise is known to enhance production of cytokines, although repeated exercise is demonstrated to attenuate the cellular response to inflammatory stimuli and inflammatory cytokines (Ardies, 2002).

J. Prostaglandins

Prostaglandins are unsaturated fatty acids synthesized from phospholipids and arachidonic acid by means of a cyclooxygenase enzyme (Zambraski et al, 1986). There are several types of prostaglandins which affect colonic function: PGE₂, which increases the rate of colonic cell proliferation and decreases colonic motility and PGF, which is an antagonist of these actions (Colditz et al, 1997; McTiernan et al, 1998). Biopsy samples taken from patients with colon polyps and/or colon adenocarcinomas revealed synthesis of more PGE₂ than controls (Pugh and Thomas, 1994). Physical activity may alter prostaglandin levels by producing high levels of Ca²⁺ and elevated levels of bradykinin during muscle

contraction, thereby stimulating phospholipase A and leading to increases in arachidonic acid metabolites including PGE2 and PGI2. Exercise also causes high intracellular pressure and may facilitate the dialysis of PGE2 and PGI2 to skeletal muscle interstitial fluid (Karamouzis et al, 2001; Karamouzis et al, 2001). Although experimental studies have found changes in prostaglandin levels in the blood with dynamic exercise, no study has been published on prostaglandin concentrations in the colonic mucosa following exercise (Quadrilatero and Hoffman-Goetz, 2003).

VI. Clinical implications

Our review has shown that there is limited evidence for the efficacy of exercise in reducing the risk of recurrence or early mortality in cancer survivors. Consequently, exercise should not be recommended to cancer survivors as a therapy to reduce their risk of recurrence or extend survival. Such recommendations will require compelling evidence from well-controlled observational studies and intervention trials. There is, however, good preliminary evidence that exercise may enhance QOL in cancer survivors, especially breast and prostate cancer survivors (Courneya, 2003). Based on this preliminary evidence, as well as our own clinical experience, we recommend exercise to otherwise healthy cancer survivors as does the American Cancer Society (Brown et al, 2003). There are several special precautions for cancer survivors, however, and the reader is referred to our previous published guidelines for these safety issues (Courneya et al, 2002; Courneya et al, 2002).

Exercise during adjuvant therapy is a major struggle for cancer survivors (e.g., Courneya and Friedenreich, 1997) but we still feel benefits can be realized (Courneya, 2003). We recommend low to moderate intensity exercise performed 3 to 5 days per week for 20-30 minutes each time, depending on baseline fitness levels and treatment toxicities. The exercise should be moderate intensity in the range of 55% to 75% of maximal heart rate. Unfortunately, many cancer survivors receiving chemotherapy experience tachycardia, which makes heart rate alone an unreliable indicator of exercise intensity. Consequently, we recommend that intensity also be monitored with a rating of perceived exertion scale (e.g., Borg, 1998) using the range of "somewhat hard" to "hard". The preferred exercise choice in cancer survivors is walking (Jones and Courneya, 2002) and this activity will likely be sufficient to meet the recommended intensity for most cancer survivors on adjuvant therapy. Exercise progression in cancer survivors during adjuvant therapy is unpredictable and not always linear given the accumulating side effects of most cancer therapies. We recommend that cancer survivors exercise to tolerance including reducing intensity and performing exercise in shorter durations (e.g., 10 minutes) if needed.

Posttreatment, most cancer survivors can probably be recommended the public health guidelines from the American College of Sports Medicine and the United States Centers for Disease Control (Pate et al, 1995). These organizations propose two different prescriptions for achieving health through physical activity. The more

traditional prescription is to perform at least 20 minutes of continuous vigorous intensity exercise (i.e., 80% of maximal heart rate) on 3 days per week. The alternative prescription is to accumulate at least 30 minutes of moderate intensity exercise (i.e., 60%-80% of maximal heart rate) in durations of at least 10 minutes on most (i.e., at least 5), preferably all, days of the week. Exercise trials in cancer survivors have tended to follow the traditional prescription but both prescriptions should yield health benefits.

VII. Future research directions

Research on exercise and clinical endpoints in cancer survivors is in its infancy and much remains to be done. To begin, we need good epidemiological research with valid measures of physical activity and complete control of potential confounders to examine the associations between physical activity and cancer recurrence, cancer-specific mortality, and all-cause mortality in various cancer survivor cohorts. We also need RCTs to examine the effects of exercise on the purported biologic mechanisms of recurrence and mortality in cancer survivors (e.g., immune function, sex steroid hormones, peptide hormones, energy balance). These first generation studies will provide the rationale and clarify the research priorities for large scale RCTs that will examine the effects of exercise on the clinical cancer endpoints. Lastly, we need studies to examine the potential interactions between exercise and cancer therapies.

VIII. Summary

Advances in early detection and medical treatments have had a significant impact on cancer survival. These advances have paved the way for the examination of lifestyle factors, such as physical activity, as a further means for reducing recurrence rates and extending survival in this population. In this paper, we reviewed evidence for the potential role of exercise in affecting clinical endpoints in cancer survivors. Our review showed that research on this topic is extremely limited. Evidence from other populations, however, suggests that it is possible that exercise could positively affect clinical endpoints in cancer survivors. Moreover, the effects of exercise on the purported mechanisms of clinical benefit for cancer endpoints provide biological plausability. Despite the limited evidence for a role of exercise in cancer survival, however, we still recommend exercise to cancer survivors based on preliminary evidence for a quality of life benefit. Future directions for research are such that the most basic questions on this topic need to be answered.

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