Commentary

Cancer Prevention Research

Physical Inactivity and Low Fitness Deserve More Attention to Alter Cancer Risk and Prognosis

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Abstract

Sedentary lifestyle is associated with elevated cancer risk whereas regular physical activity (PA) and high cardiorespiratory fitness (CRF) have the opposite effect, with several biologic mechanisms mediating such associations. There is a need for lifestyle interventions aimed at increasing the PA levels and CRF of the general population and particularly cancer survivors. Furthermore, provocative data suggest a dose-dependent benefit of increasing levels of PA and/or CRF against cancer risk or mortality. Thus, current PA guidelines (≥150 min/wk of moderate-to-vigorous PA) may not be sufficiently rigorous for preventing cancer nor for extending cancer survivorship. Research targeting this issue is urgently needed. Promoting regular PA along with monitoring indicators of CRF and adiposity may provide powerful strategies to prevent cancer in populations, help patients with cancer more effectively deal with their disease and enhance secondary prevention programs in those who are affected by cancer. *Cancer Prev Res; 8(2); 105–10. ©2014 AACR.*

Physical Inactivity and Low Fitness Increase Cancer Risk and Mortality

Physical activity (PA) is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (1). In turn, physical fitness is "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy (leisure) pursuits and to meet unforeseen emergencies" (2). The PA behaviors that may be measured in health promotion studies include: frequency, duration, intensity or type of PA, and domains or settings in which the activity is performed such as leisure time PA, occupational activity, active commuting, incidental energy expenditure, and sedentary behavior settings (3).

PA is the only behavioral intervention that has been proven useful to increase cardiorespiratory fitness (CRF), it should be recognized that CRF is a phenotype that has a strong genetic component in populations with heritability coefficients of the order of 50% after adjustments for age, gender, body mass and body composition (4–6). The gold standard measure of CRF is maximal oxygen uptake (VO_{2max}), typically expressed as follows: milliliters of O_2 uptake · per kilogram of body mass/minute, or metabolic equivalents (MET), in which 1 MET = 3.5 mL O_2 uptake· per kilogram of body mass/minute (7). See Table 1 for explanation of the MET concept and how this translates into the percentage of an individual's maximum CRF.

VO_{2max} can be assessed with direct or indirect methods. Direct measures are obtained by ventilatory gas analysis at maximal exertion during a graded exercise ergometry test (8, 9) whereas indirect methods estimate VO_{2max} from maximal exercise duration, the peak workload and/or heart rate (HR) responses reached during submaximal or maximal exercise ergometry, or the time required to walk or run a distance (9). Although other nonexercise-based methods have been developed (10), those containing an exercise component (8, 9) remain the definitive standard.

According to PA guidelines issued by the U.S. Department of Health and Human Services (11) and the World Health Organization (12), adults should undertake ≥150 min/wk of moderate-to-vigorous PA (MVPA). On the other hand, sedentary behaviors are defined as "any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting or reclining posture" according to the Sedentary Behaviour Research Network (SBRN), whereas "physical inactivity" refers to those who perform insufficient amounts of MVPA (i.e., <150 min/wk; ref. 13).

The link between levels of PA, CRF, and cancer risk is receiving growing attention. This is a topic of paramount importance in modern medicine because approximately one third of adults worldwide are currently inactive and the endemic inactivity trend starts in early life (14). In contrast, regular PA raises metabolic rate and increases CRF via increases in cardiovascular function (15), muscle mitochondrial biogenesis and oxidative enzyme activity, particularly of the enzymes responsible for fat oxidation, as well as

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Table 1. Explanation of the intensity of PA expressed using the MET concept and how this translates into the percentage of an individual's maximal CRF. Extracted from (refs. 2 and 73)

	Relative intensity		Absolute intensity (in MET)		
Classification of exercise intensity	HR_{max} (%)	Maximal CRF (%)	Young (20–39 years)	Middle-aged (40–64 years)	Older (≥65 years)
Very light	<57	<37	<2.4	<2.0	<1.6
Light	57–63	37–45	2.4–4.7	2.0–3.9	1.6–3.1
Moderate	64–76	46–63	4.8–7.1	4.0–5.9	3.2–4.7
Vigorous	77–95	64–90	7.2–10.1	6.0–8.4	4.8–6.7
Near-maximal to maximal	≥96	≥91	≥10.2	≥8.5	≥6.8

NOTE: 1 MET equals an oxygen consumption of 3.5 mL/kg/min, which is the average resting energy expenditure for humans. MET-hour is an index of energy expenditure that quantifies the total amount of PA performed in a standardized manner across individuals and types of activities (U.S. Department of Health and Human Services, 2008). It is calculated as the product of the number of mean MET associated with one PA and the number of hours the PA was performed. For example, jogging (at 7 METs) for 1 hour: 7 METs × 1 hour = 7 MET-hour.

Abbreviation: HR_{max} (maximum heart rate, which on average and for simplicity purposes, could be estimated as 220 − age in years).

decreases in body adiposity (16–19). Thus, regular PA is recommended as an important part of a healthy lifestyle as well as for weight management by virtually all public health agencies and scientific organizations (20–24). In contrast, physical inactivity has been estimated to contribute more than 10% of the disease burden of two of the most prevalent cancers among westerners, that is, breast and colon (accounting for 13.8% and 14.9% of the burden, respectively, among the Spanish population and 12.4% and 12%, respectively, in the United States; ref. 25). Besides the beneficial effects of exercise on energy balance, high levels of regular PA *per se* have also been shown to decrease the risk of cancer (22, 23, 26–32) as well as the risk of mortality among cancer survivors, particularly of breast and colorectal cancer (33).

Engaging in 8.75 or more MET-hour/week of recreational PA (equivalent to ∼150 min/wk of brisk walking) was associated with lower colorectal cancer–related mortality compared with <3.5 MET-hour/week, whereas longer leisure time spent sitting was associated with higher risk of death from colorectal cancer (34). A meta-analysis of recreational PA showed that the risk of colorectal cancer decreased by 6% per MET-hour/week, along with a 12% decreased risk per 30 min/d of recreational PA for colon cancer, by decreasing inflammation, and reducing insulin resistance resulting in lower circulating insulin levels (35). Another meta-analysis that compared highest versus lowest leisure time PA in the prevalence of colon cancer showed a 20% decreased risk in men and a 14% decreased risk in women (36). Moreover, it has been shown that breast cancer and cancers of the reproductive system are less prevalent in women who had been athletes in college compared with nonathletic controls (37). There is also evidence of a lower risk of breast cancer with higher levels of regular PA, with a dose-dependent relationship (36, 38, 39).

A recent meta-analysis from our group has shown a 40% lower standard mortality ratio due to cancer in those engaging in the highest PA levels, that is, elite athletes of various sport disciplines ($n = 12{,}119$, mostly men), including "*Tour de France*" finishers, compared with the general population (40). Although the lower mortality in elite athletes could be associated with an overall healthier lifestyle, for example, reduced tobacco use, the data are compatible with the notion that regular PA confers protection against a number of cancers. Taken together, the studies outlined above are suggestive of a potential dose–response relationship.

Potential Biologic Underpinnings

The biologic mechanisms responsible for the potential antitumorigenic effects of PA (independently of its influence on adiposity) remain to be elucidated, yet provocative data suggest that contracting muscle-derived molecules exerting either paracrine or endocrine effects, known as "myokines," are strong candidates for mediating the PA anticancer effects. For instance, secreted protein acidic and rich in cysteine (SPARC) is a matricellular protein that regulates cell proliferation and migration (41), and was recently identified as a myokine (42, 43) whose expression increases with regular PA training (43). SPARC, which is in fact a potential target in cancer immunotherapy (44), might mediate the preventive effects of exercise on colon cancer by suppressing the formation of aberrant crypt foci through stimulation of apoptosis via caspase-3 and -8 (42). Circulating and muscle-transcript levels of S100A8–S100A9 complex (calprotectin) increase with acute PA bouts (45–48). One could also speculate that muscle-derived calprotectin might be cancer protective as shown by its ability to induce apoptosis in certain tumor lines (49), including colon cancer lines (50), or to inhibit matrix metalloproteinases associated with cancer invasion/metastasis (51). PA is also a powerful inducer of muscle and systemic autophagy that has been suggested to serve as a tumor-suppressor pathway (52–54).

Although the focus of this commentary is on PA and CRF, it is important to acknowledge that PA (particularly vigorous PA) can contribute to reduction in adipose tissue, which itself can be an important contributor to decreased cancer risk, morbidity, and mortality (55–59). Thus, the reduction in adipose tissue associated with PA could potentially decrease cancer-promoting potential by reducing multiple mediators, including sex steroid hormones, insulin-like growth factors, inflammatory cytokines, and adipocytokines (60–64). Reducing adiposity could also decrease mechanical issues such as those leading to gastroesophageal reflux disease, which predisposes to esophageal adenocarcinoma (65–66). In fact, the link between overweight/obesity and cancer is of significant concern, especially when taking into consideration the increasing incidence of both disorders (67–69). Thus, as illustrated in Fig. 1, the combination of obesity, physical inactivity, and low fitness levels can be considered a toxic triad promoting cancer incidence and mortality that should be amenable to lifestyle alterations such as PA, which could potentially improve all three.

Cancer Survivors Do Not Take Full Advantage of the PA and CRF Benefits

In cohorts of U.S. cancer survivors in which PA was measured objectively (i.e., using accelerometry), mean MVPA levels were clearly below the recommended 150 min/wk threshold, that is, approximately 26 (breast) and approximately 42 (prostate) min/wk (70–71). Moreover, in a recent U.S. National Health and

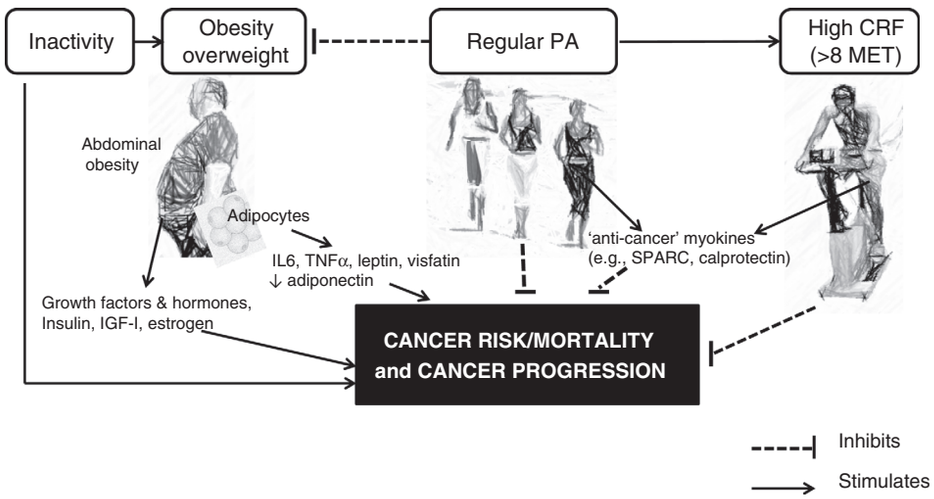

Figure 1.
Summary of the interplay between cancer and obesity, PA, and CRF. Abbreviations: IL6, interleukin 6; TNFα, tumor necrosis α.

Nutrition Examination Survey (NHANES) of more than 7 million cancer survivors, only 4.5% met the PA recommendation whereas obesity prevalence was 33.9% (72).

In contrast, it was recently reported that 94% of a cohort of Spanish cancer survivors ($n = 204$) performed more than 150 min/wk of MVPA (73). And yet their body weight status [mean body mass index (BMI) = 27.9 kg/m^2, obesity prevalence = 32.7%] was similar to that of the four inactive U.S. cohorts (74). Unfortunately, despite the fact that the PA levels of the abovementioned Spanish cohort were relatively high compared with current guidelines, this was not accompanied by a "healthy" cardiometabolic profile. Indeed the mean CRF of this cohort (men and women with a mean age of 54 years) reached only 7.7 MET and about 1 in 2 cancer survivors did not reach a CRF of 8 MET (73). These results are consistent with those of a meta-analysis showing that CRF was substantially lower in women (mean age of the studied cohorts ~45–60 years) with a history of breast cancer compared with healthy women, especially in the post-adjuvant setting (75). The findings of such low CRF levels in cancer survivors deserve more research because any value below 8 MET is indicative of an increased risk for mortality and cardiovascular events in men and women ages 40 to 60 years on average (73, 76), and cardiovascular disease is the leading cause of long-term morbidity and mortality among long-term cancer survivors (77). Furthermore, there is also epidemiologic evidence supporting a protective role of CRF against bowel, colorectal, and liver cancer–related deaths in men over a wide age range (20–88 years), with those with a CRF level below 8 MET being characterized by over a 3-fold higher risk of dying from bowel cancer compared with those with higher capacities (≥11 MET; ref. 78).

Although there is convincing evidence that CRF is negatively associated with morbidity and mortality in men and women, independently of other risk factors, the clinical relevance of CRF is frequently overlooked in medical settings (25). In young and middle-aged adults, a CRF above 8 MET may be needed to provide protective benefits in cancer survivors. In this regard, a healthy body weight (BMI < 25) would be a clear advantage. For instance, a 10% reduction in the BMI of the male cancer survivors of the abovementioned Spanish cohort would have translated into CRF levels of 8 and 11 MET in 66% and 28% of the subjects, respectively. Thus, regular PA and diet interventions are needed to achieve a true weight loss as well as a healthy cardiometabolic profile (79).

With regards to PA, current MVPA guidelines (>150 min/wk) may not be sufficient to experience all the benefits that are generated by a physically active lifestyle. We propose that future interventions aimed at primary and secondary cancer prevention should focus on vigorous PA (≥6 MET, e.g., very brisk walking to increase CRF even more and to improve the odds of meaningful weight loss; ref. 80).

Summary and Future Recommendations

In summary, regular PA and high CRF are associated with a lower incidence and better prognosis of cancer. In light of the available evidence, tantalizing but admittedly incomplete, is it appropriate at this time to call for a more proactive approach to primary and secondary prevention of cancer? We believe that a call for more proactive measures is justified on two fronts.

First, research is needed to clarify a number of issues and provide a stronger foundation in which more evidence is warranted. For instance, what are differential CRF values between cancer survivors and nonsurvivors? What are normative CRF values for cancer survivors in each gender across the lifespan? Are demanding PA programs (perhaps focusing on vigorous PA or combining PA with other lifestyle changes, especially diet) feasible in cancer survivors and do they actually achieve "healthy" levels of CRF as currently defined [>8 MET for middle-aged (40–60 years) men/women] or adiposity? Given that current MVPA guidelines emphasize >150 min/wk of moderate intensity PA, what is the PA dose recommended for cancer survivors aimed at achieving a healthy cardiometabolic profile and optimizing secondary prevention?

Second, there is an urgent need for lifestyle interventions aimed at increasing PA levels and CRF not only in the general population but particularly in cancer survivors. Although current guidelines focused on >150 min/wk of moderate intensity PA may be a valuable and practical public health formula, it should be investigated to determine whether higher PA intensity, duration, or frequency could achieve hidden benefits in cancer survivors. This is obviously an issue that needs to be resolved though high quality and highly targeted research to evaluate both the short- and long-term effects of eliminating physical inactivity and increasing CRF.

More importantly, just as developmental chemotherapy research evaluates progressively higher doses of anticancer agents, it is time to evaluate benefits of vigorous compared with moderate PA. Short-term effects should focus on response and tolerance to therapy, hospital utilization as well as on potential changes in CRF, BMI as well as mediators and biomarkers such as growth-promoting hormones, inflammatory cytokines, antitumor, and anti-inflammatory myokines. Studies on long-term effects are needed to focus on effects of vigorous PA on parameters such as remission duration, time to recurrence and cancer specific and overall survival. Such interventions are difficult to support, because in the present climate, well-conducted interventions are very expensive and require budgets well over caps currently imposed by most funding organizations. Nonetheless, because this research is so critically important to patient outcomes, there may be some basis for optimism in the relatively newly established Patient-Centered Outcomes Research Institute mission to fund comparative clinical effectiveness research authorized in the United States as part of the Patient Protection and Affordable Care Act of 2010 (81).

In the meantime, although we seek to develop more evidence based research results, oncologists and health care personnel should be made more aware of the potential downside associated with obesity, low PA levels, and poor CRF. More importantly, recommending measures to improve these parameters and monitoring PA (such as recently recommended by the American Heart Association; refs. 82, 83) along with indicators of CRF and adiposity in routine follow-up examinations would provide the information needed for healthcare professionals to consider changing their approach and favor the implementation of effective lifestyle interventions.

Disclosure of Potential Conflicts of Interest

C. Bouchard is a consultant/advisory board member for Weight Watchers International. No potential conflicts of interest were disclosed by the other authors.

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