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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 biological 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. Further, 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/week 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 cancer patients more effectively deal with their disease and enhance secondary prevention programs in those who are affected by cancer.

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1. 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 where 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 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 · kilograms of body mass^{-1} · minute^{-1}, or metabolic equivalents (METs), where 1 MET = 3.5 ml O_2 uptake · kilograms of body mass^{-1} · minute^{-1} (7). See Table 1 for explanation of the MET concept and how this translates into % 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). While other non exercise based methods have been developed (10) those containing an exercise component (8, 9) remain the definitive standard.

According to PA guidelines issued by the US Department of Health and Human Services (11) and the World Health Organization (12), adults should undertake ≥150min/week 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) whilst "physical inactivity" refers to those who perform insufficient amounts of MVPA (i.e., <150min/week) (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 since ~1/3 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 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 2 of the most prevalent cancers among westerners, i.e., 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 US)(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 ~150min/week of brisk walking) was associated with lower colorectal cancer 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/day 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 non-athletic 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, i.e., elite athletes of various sport disciplines (n=12,119, mostly men), including *'Tour de France'* finishers, compared with the general population (40). While the lower mortality in elite athletes could be associated with an overall healthier lifestyle, for example reduced tobacco use, the data is 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.

2. Potential biological underpinnings

The biological mechanisms responsible for the potential anti-tumorigenic 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 anti-cancer 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 which has been suggested to serve as a tumor suppressor pathway (52–54).

While 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 physical activity 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 Figure 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.

3. Cancer survivors do not take full advantage of the PA and CRF benefits

In cohorts of US cancer survivors in which PA was measured objectively (i.e., using accelerometry), mean MVPA levels were clearly below the recommended 150 min/week-threshold, i.e., ~26 (breast) and ~42 (prostate) min/week (70–71). Moreover, in a recent US National Health and Nutrition Examination Survey (NHANES) of over 7 million cancer survivors, only 4.5% met the PA recommendation while 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 150min/week of MVPA (73). And yet their body weight status (mean BMI = 27.9 kg/m^2, obesity prevalence = 32.7%) was similar to that of the 4 inactive US cohorts (74). Unfortunately, despite the fact that the PA levels of the abovementioned Spanish cohort was relatively high compared to 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 aged 40–60 years on average (73, 76), and cardiovascular disease is the leading cause of long-term morbidity and mortality among long-term cancer survivors (77). Further, there is also epidemiological evidence supporting a protective role of CRF against bowel, colorectal and liver cancer 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 to those with higher capacities (≥ 11 MET) (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 cardiorespiratory fitness 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 above mentioned 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 (>150min/week) 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 in order to increase CRF even more and to improve the odds of meaningful weight loss (80).

4. Summary and future recommendations

In summary, regular PA and high cardiorespiratory fitness 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 where more evidence is warranted. For instance, what are differential CRF values between cancer survivors and non-survivors? 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/week 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/week 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 to 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, since in the

present climate, well conducted interventions are very expensive and require budgets well over caps currently imposed by most funding organizations. Nonetheless, since 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 (PCORI) 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, while 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 (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.

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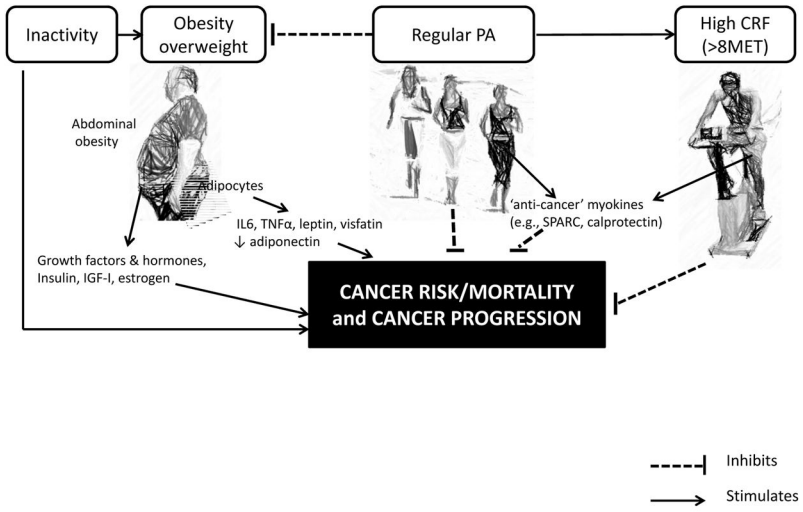

Figure 1.

Summary of the interplay between cancer and obesity, physical activity (PA), and cardiorespiratory fitness (CRF). Abbreviations: IL6, interleukin 6; SPARC, secreted protein acidic and rich in cysteine; TNFα, tumor necrosis α.

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Table 1

Explanation of the intensity of physical activity (PA) expressed using the MET (metabolic equivalent) concept and how this translates into % of an individual's maximal cardiorespiratory capacity (CRF). Extracted from (2, 73)

	RELATIVE INTENSITY		ABSOLUTE INTENSITY (in MET)		
CLASIFICATION OF EXERCISE INTENSITY	**%HRmax**	**% of 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 (US 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 x 1 hour = 7 MET-hour.

Abbreviation: HRmax (maximum heart rate, which on average and for simplicity purposes, could be estimated as 220 minus age in years)