Published OnlineFirst November 21, 2014; DOI: 10.1158/1940-6207.CAPR-14-0320

Commentary

Cancer Prevention Research

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

Fabian Sanchis-Gomar[1,2], Alejandro Lucia[3,4], Thomas Yvert[5], Ana Ruiz-Casado[6], Helios Pareja-Galeano[1,2], Alejandro Santos-Lozano[3,7], Carmen Fiuza-Luces[3,4], Nuria Garatachea[3,8], Giuseppe Lippi[9], Claude Bouchard[10], and Nathan A. Berger[11]

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

[1]Faculty of Medicine, Department of Physiology, University of Valencia, Valencia, Spain. [2]Fundación Investigación Hospital Clínico Universitario/INCLIVA. Spain. [3]Research Institute of Hospital 12 de Octubre ("i+12"), Madrid, Spain. [4]European University, Madrid, Spain. [5]School of Doctorate Studies and Research, Universidad Europea de Madrid, Madrid, Spain. [6]Department of Oncology, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain. [7]Department of Biomedical Sciences, University of León, León, Spain. [8]Faculty of Health and Sport Sciences, University of Zaragoza, Huesca, Spain. [9]Laboratory of Clinical Chemistry and Hematology, Academic Hospital of Parma, Parma, Italy. [10]Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, Louisiana. [11]Center for Science, Health and Society, Case Comprehensive Cancer Center, Case Western Reserve University, School of Medicine, Cleveland, Ohio.

Corresponding Author: Nathan A. Berger, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106-4971. Phone: 216-368-4084; Fax: 216-368-3244; E-mail: nab@case.edu

doi: 10.1158/1940-6207.CAPR-14-0320

Published OnlineFirst November 21, 2014; DOI: 10.1158/1940-6207.CAPR-14-0320

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

Published OnlineFirst November 21, 2014; DOI: 10.1158/1940-6207.CAPR-14-0320

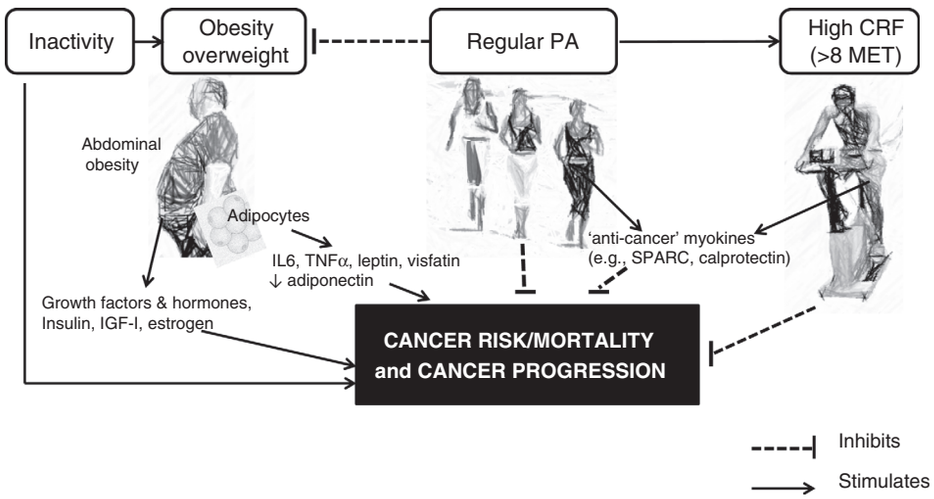

Figure 1.
Summary of the interplay between cancer and obesity, PA, and CRF. Abbreviations: IL6, interleukin 6; TNFα, tumor necrosis α.

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.

Published OnlineFirst November 21, 2014; DOI: 10.1158/1940-6207.CAPR-14-0320

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.

Authors' Contributions

Conception and design: F. Sanchis-Gomar, A. Lucia, A. Santos-Lozano, N.A. Berger

Development of methodology: A. Lucia

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Garatachea, C. Bouchard

Writing, review, and/or revision of the manuscript: F. Sanchis-Gomar, A. Lucia, T. Yvert, A. Ruiz-Casado, H. Pareja-Galeano, A. Santos-Lozano, C. Fiuza-Luces, N. Garatachea, G. Lippi, C. Bouchard, N.A. Berger

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Garatachea

Grant Support

This work was supported, in part, by Fondo de Investigaciones Sanitarias FIS; # PI12/00914 (to A. Lucia); John W. Barton Sr. Chair in Genetics and Nutrition and NIH HL-045670 (to C. Bouchard); Hanna-Payne Professor Experimental Medicine, Ellison Medical Foundation, and NIH grants P50 CA150964 and U54 CA163060 (to N.A. Berger).

Received September 23, 2014; revised October 30, 2014; accepted November 11, 2014; published OnlineFirst November 21, 2014.

References

1. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100:126–31.
2. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334–59.
3. Bauman A, Phongsavan P, Schoeppe S, Owen N. Physical activity measurement—a primer for health promotion. Promot Educ 2006;13:92–103.
4. Lesage R, Simoneau JA, Jobin J, Leblanc J, Bouchard C. Familial resemblance in maximal heart rate, blood lactate and aerobic power. Human heredity 1985;35:182–9.
5. Bouchard C, Lesage R, Lortie G, Simoneau JA, Hamel P, Boulay MR, et al. Aerobic performance in brothers, dizygotic, and monozygotic twins. Med Sci Sports Exerc 1986;18:639–46.
6. Bouchard C, Daw EW, Rice T, Perusse L, Gagnon J, Province MA, et al. Familial resemblance for VO2max in the sedentary state: the HERITAGE family study. Med Sci Sports Exerc 1998;30:252–8.
7. Jurca R, Jackson AS, LaMonte MJ, Morrow JR Jr, Blair SN, Wareham NJ, et al. Assessing cardiorespiratory fitness without performing exercise testing. Am J Prev Med 2005;29:185–93.
8. Davis JA. Direct determination of aerobic power. In: Maud PJ, Foster C, editors. Physiological assessment of human fitness. Champaign IL: Human Kinetics; 1995. p. 9–17.
9. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. Sixth Edition. Philadelphia: Wilkinson LW. 2000.
10. Stamatakis E, Hamer M, O'Donovan G, Batty GD, Kivimaki M. A non-exercise testing method for estimating cardiorespiratory fitness: associations with all-cause and cardiovascular mortality in a pooled analysis of eight population-based cohorts. Eur Heart J 2012;34:750–8.
11. Physical Activity Guidelines for Americans. 2008. Available from: http://www.health.gov/paguidelines.
12. World-Health-Organization. Global recommendations on physical activity for health. Switzerland. 2010. Available from: http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf.
13. Sedentary Behaviour Research N. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours." Appl Physiol Nutr Metab 2012;37:540–2.
14. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet 2012;380:247–57.
15. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology 2013;28:330–58.
16. Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. J Appl Physiol 1984;56:831–8.
17. Hermansen L, Wachtlova M. Capillary density of skeletal muscle in well-trained and untrained men. J Appl Physiol 1971;30:860–3.
18. Ingjer F. Capillary supply and mitochondrial content of different skeletal muscle fiber types in untrained and endurance-trained men. A histochemical and ultrastructural study. Eur J Appl Physiol Occup Physiol 1979;40:197–209.
19. Essen B, Hagenfeldt L, Kaijser L. Utilization of blood-borne and intramuscular substrates during continuous and intermittent exercise in man. J Physiol 1977;265:489–506.
20. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert panel on the identification, evaluation, and treatment of overweight in adults. Am J Clin Nutr 1998;68:899–917.
21. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1423–34.
22. Tsigos C, Hainer V, Basdevant A, Finer N, Fried M, Mathus-Vliegen E, et al. Management of obesity in adults: European clinical practice guidelines. Obes Facts 2008;1:106–16.

23. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series 894). 2000. Available from: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/
24. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2007. Available from: http://www.dietandcancerreport.org/cancer_resource_center/downloads/Second_Expert_Report_full.pdf
25. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012;380:219–29.
26. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med 2008;42:636–47.
27. Irwin ML. Physical activity interventions for cancer survivors. Br J Sports Med 2009;43:32–8.
28. Gander J, Lee DC, Sui X, Hebert JR, Hooker SP, Blair SN. Self-rated health status and cardiorespiratory fitness as predictors of mortality in men. Br J Sports Med 2011;45:1095–100.
29. Laukkanen JA, Rauramaa R, Makikallio TH, Toriola AT, Kurl S. Intensity of leisure-time physical activity and cancer mortality in men. Br J Sports Med 2009;45:125–9.
30. Campbell KL, Neil SE, Winters-Stone KM. Review of exercise studies in breast cancer survivors: attention to principles of exercise training. Br J Sports Med 2012;46:909–16.
31. Abioye AI, Odesanya MO, Ibrahim NA. Physical activity and risk of gastric cancer: a meta-analysis of observational studies. Br J Sports Med. 2014 Jan 16. doi: 10.1136/bj sports -2013-092778 [Epub ahead of print].
32. Winters-Stone KM, Neil SE, Campbell KL. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. Br J Sports Med 2014;48:987–95.
33. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann Oncol 2014;25:1293–311.
34. Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. J Clin Oncol 2013;31:876–85.
35. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. Food, nutrition, physical activity, and the prevention of colorectal cancer. 2011. Available form: http://www.dietandcancerreport.org/cancer_resource_center/downloads/cu/Colorectal-Cancer-2011-Report.pdf.
36. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. Food, nutrition, physical activity, and the prevention of breast cancer. 2010. Available form: http://www.wcrf.org/sites/default/files/Breast-Cancer-Survivors-2014-Report.pdf.
37. Frisch RE, Wyshak G, Albright NL, Albright TE, Schiff I, Witschi J, et al. Lower lifetime occurrence of breast cancer and cancers of the reproductive system among former college athletes. Am J Clin Nutr 1987;45:328–35.
38. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat 2013;137:869–82.
39. Goncalves AK, Dantas Florencio GL, Maisonnette de Atayde Silva MJ, Cobucci RN, Giraldo PC, Cote NM. Effects of physical activity on breast cancer prevention: a systematic review. J Phys Act Health 2014;11:445–54.
40. Garatachea N, Santos-Lozano A, Sanchis-Gomar F, Fiuza-Luces C, Pareja-Galeano H, Emanuele E, et al. Elite athletes live longer than the general population: a meta-analysis. Mayo Clin Proc 2014;89:1195–2000.
41. Brekken RA, Sage EH. SPARC, a matricellular protein: at the crossroads of cell-matrix communication. Matrix Biol 2001;19:816–27.
42. Aoi W, Naito Y, Takagi T, Tanimura Y, Takanami Y, Kawai Y, et al. A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. Gut 2013;62:882–9.
43. Norheim F, Raastad T, Thiede B, Rustan AC, Drevon CA, Haugen F. Proteomic identification of secreted proteins from human skeletal muscle cells and expression in response to strength training. Am J Physiol Endocrinol Metab 2011;301:E1013–21.
44. Inoue M, Senju S, Hirata S, Ikuta Y, Hayashida Y, Irie A, et al. Identification of SPARC as a candidate target antigen for immunotherapy of various cancers. Int J Cancer 2010;127:1393–403.
45. Mortensen OH, Andersen K, Fischer C, Nielsen AR, Nielsen S, Akerstrom T, et al. Calprotectin is released from human skeletal muscle tissue during exercise. J Physiol 2008;586:3551–62.
46. Fagerhol MK, Nielsen HG, Vetlesen A, Sandvik K, Lyberg T. Increase in plasma calprotectin during long-distance running. Scand J Clin Lab Invest 2005;65:211–20.
47. Mooren FC, Lechtermann A, Fobker M, Brandt B, Sorg C, Volker K, et al. The response of the novel pro-inflammatory molecules S100A8/A9 to exercise. Int J Sports Med 2006;27:751–8.
48. Peake J, Peiffer JJ, Abbiss CR, Nosaka K, Okutsu M, Laursen PB, et al. Body temperature and its effect on leukocyte mobilization, cytokines and markers of neutrophil activation during and after exercise. Eur J Appl Physiol 2008;102:391–401.
49. Yui S, Mikami M, Yamazaki M. Purification and characterization of the cytotoxic factor in rat peritoneal exudate cells: its identification as the calcium binding protein complex, calprotectin. J Leukoc Biol 1995;58:307–16.
50. Ghavami S, Kerkhoff C, Los M, Hashemi M, Sorg C, Karami-Tehrani F. Mechanism of apoptosis induced by S100A8/A9 in colon cancer cell lines: the role of ROS and the effect of metal ions. J Leukoc Biol 2004;76:169–75.
51. Isaksen B, Fagerhol MK. Calprotectin inhibits matrix metalloproteinases by sequestration of zinc. Mol Pathol 2001;54:289–92.
52. Levine B. Cell biology: autophagy and cancer. Nature 2007;446:745–7.
53. He C, Bassik MC, Moresi V, Sun K, Wei Y, Zou Z, et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. Nature 2012;481:511–5.
54. He C, Sumpter R Jr, Levine B. Exercise induces autophagy in peripheral tissues and in the brain. Autophagy 2012;8:1548–51.
55. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
56. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569–78.
57. Azvolinsky A. Cancer risk: the fat tissue-BMI-obesity connection. J Natl Cancer Inst 2014;106:dju100.
58. Bhaskaran K, Douglas I, Forbes H, Dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 2014;384:755–65.
59. Kmietowicz Z. Overweight and obesity are linked to 10 common cancers and more than 12 000 UK cases. BMJ 2014;349:g5183. doi: 10.1136/bmj.g5183.
60. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.
61. Drew JE. Molecular mechanisms linking adipokines to obesity-related colon cancer: focus on leptin. Proc Nutr Soc 2012;71:175–80.
62. Gallagher EJ, LeRoith D. Minireview: IGF, Insulin, and Cancer. Endocrinology 2011;152:2546–51.
63. Hursting SD, Berger NA. Energy balance, host-related factors, and cancer progression. J Clin Oncol 2010;28:4058–65.
64. Berger NA. Obesity and cancer pathogenesis. Ann N Y Acad Sci 2014;1311:57–76.
65. Anand G, Katz PO. Gastroesophageal reflux disease and obesity. Rev Gastroenterol Disord 2008;8:233–39.
66. Leidner R, Chak A. Obesity and the pathogenesis of Barrett's esophagus. In: Markowitz SD, Berger NA, editors. Energy balance and gastrointestinal cancer, chapter 5. New York: Springer 2012:77–92.
67. World Health Organization, Global database on body mass index. Available from: http://www.who.int/topics/obesity/en/.
68. World Health Organization, International agency for research on cancer, GLOBOCAN project. Available from: http://globocan.iarc.fr/Default.aspx.
69. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. J Obes 2013;2013:291546.
70. Lynch BM, Dunstan DW, Healy GN, Winkler E, Eakin E, Owen N. Objectively measured physical activity and sedentary time of breast cancer survivors, and associations with adiposity: findings from NHANES (2003–2006). Cancer Causes Control 2010;21:283–8.
71. Lynch BM, Dunstan DW, Winkler E, Healy GN, Eakin E, Owen N. Objectively assessed physical activity, sedentary time and waist circumference among prostate cancer survivors: findings from the National Health and

Published OnlineFirst November 21, 2014; DOI: 10.1158/1940-6207.CAPR-14-0320

Nutrition Examination Survey (2003–2006). Eur J Cancer Care 2011;20:514–9.
72. Smith WA, Nolan VG, Robison LL, Hudson MM, Ness KK. Physical activity among cancer survivors and those with no history of cancer- a report from the National Health and Nutrition Examination Survey 2003–2006. Am J Transl Res 2011;3:342–50.
73. Ruiz-Casado A, Verdugo AS, Solano MJ, Aldazabal IP, Fiuza-Luces C, Alejo LB, et al. Objectively assessed physical activity levels in Spanish cancer survivors. Oncol Nurs Forum 2014;41:E12–20.
74. Jovanovic M, Soldatovic I, Janjic A, Vuksanovic A, Dzamic Z, Acimovic M, et al. Diagnostic value of the nuclear matrix protein 22 test and urine cytology in upper tract urothelial tumors. Urol Int 2011;87:134–7.
75. Peel AB, Thomas SM, Dittus K, Jones LW, Lakoski SG. Cardiorespiratory fitness in breast cancer patients: a call for normative values. J Am Heart Assoc 2014;3:e000432.
76. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 2009;301:2024–35.
77. Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, et al. SEER Cancer Statistics Review, 1975–2006, Bethesda, MD: National Cancer Institute. Available from: http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009.
78. Peel JB, Sui X, Matthews CE, Adams SA, Hebert JR, Hardin JW, et al. Cardiorespiratory fitness and digestive cancer mortality: findings from the aerobics center longitudinal study. Cancer Epidemiol Biomarkers Prev 2009;18:1111–7.
79. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA 2007;297:2081–91.
80. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. Cochrane Database Syst Rev 2006:CD003817.
81. About Us PCORI. Available from: http://www.pcori.org/about-us.
82. Strath SJ, Kaminsky LA, Ainsworth BE, Ekelund U, Freedson PS, Gary RA, et al. Guide to the assessment of physical activity: clinical and research applications: a scientific statement from the American Heart Association. Circulation 2013;128:2259–79.
83. US Department of Health and Human Services. Physical Activity Guidelines for Americans. 2008. [Accesed September 18, 2014]. Available from: http://www.health.gov/paguidelines/pdf/paguide.pdf

Published OnlineFirst November 21, 2014; DOI: 10.1158/1940-6207.CAPR-14-0320

Cancer Prevention Research

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

Fabian Sanchis-Gomar, Alejandro Lucia, Thomas Yvert, et al.

Cancer Prev Res 2015;8:105-110. Published OnlineFirst November 21, 2014.