Cancer Causes & Control (2018) 29:7–11
https://doi.org/10.1007/s10552-017-0983-y

COMMENTARY

Can we HIIT cancer if we attack inflammation?

Efthymios Papadopoulos[1,2] · **Daniel Santa Mina**[1,2]

Received: 6 July 2017 / Accepted: 16 November 2017 / Published online: 21 November 2017

Abstract
Physical exercise offers numerous health-related benefits to individuals with cancer. Epidemiologic research has primarily been concerned with conventional exercise training that aligns with the recommendations of 150 min of moderate to vigorous physical activity per week. These recommendations are safe and effective at improving physical and psychosocial outcomes. Given the extensive evidence for generalized physical activity, researchers have begun to explore novel training regimens that may provide additional health benefits and/or improved adherence. Specifically, exercise at higher intensities may offer more or different benefits than conventional training approaches with potentially profound effects on the tumor microenvironment. This commentary focuses on the physiological effects of high-intensity interval training, also known as "HIIT," and its potential antineoplastic properties.

Keywords Cancer survivors · High-intensity interval training · Inflammation

Introduction

A cancer diagnosis is commonly accompanied by progressive physiological and psychosocial deterioration due to disease manifestation and the adverse effects of treatment. A convincing body of evidence has led to a general acceptance that exercise is a viable strategy of enhancing physical and psychosocial outcomes in individuals with cancer. Moreover, epidemiological evidence demonstrates that exercise reduces the risk of cancer recurrence and mortality [1]. The mechanistic properties of these relationships have been explored via in vitro models indicating exercise-related inhibitory effects on tumor growth and proliferation [2]. The antineoplastic effects of exercise are multifactorial and include reduced bioavailability of tumor growth factors [2], increases in p53 tumor suppressor protein [3], as well as natural killer cell mobilization and infiltration induced by epinephrine [4]. The overall evidence of benefits has underscored recommendations for exercise in people with cancer, most commonly delivered via moderate-intensity continuous training (MICT) that has established safety and effectiveness [5, 6]. However, growing research shows that exercising at higher intensities may offer different and/or additional benefits for people with cancer [7, 8]. Below, the physiological rationale for high-intensity interval training (HIIT) as a clinical tool in cancer care is introduced.

What is HIIT?

HIIT comprises a series of repeated bursts of high-intensity exercise, defined as 85–95% of peak heart rate, interspersed by periods of rest or active recovery (i.e., exercise at a lower intensity) [9]. Although most studies describe the intensity of HIIT protocols using percent of 'maximum heart rate,' 'peak heart rate' may be more precise if true physiological maximum cannot be ascertained during baseline testing. There are several forms of HIIT that vary the number and duration of the interval–recovery ratios yielding low- and high-volume protocols [7, 8]. The flexibility of HIIT protocols permits accommodation to the full range of fitness levels. While conventionally performed on a stationary cycle or treadmill, HIIT can be performed using modalities to match aerobic training preferences. Perhaps, the most advantageous aspect of HIIT from an implementation and adherence perspective is that it appears to maximize the exercise 'dose' in a short duration making it a time-efficient strategy for achieving cardiorespiratory fitness gains [7, 10]. For these

✉ Daniel Santa Mina
daniel.santamina@utoronto.ca

[1] Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, ON, Canada

[2] Cancer Rehabilitation and Survivorship, Princess Margaret Cancer Centre, Toronto, ON, Canada

reasons, HIIT has become an increasingly popular training strategy in the general population [11]. For individuals with cancer, the brevity of HIIT may be a preferred strategy for routine exercise to obviate common time-related barriers, such as medical appointments, returning to work, and daily windows of adequate energy. Beyond adherence, HIIT's unique capacity to attenuate persistent inflammatory processes that are involved in cancer initiation and progression is particularly intriguing for the cancer clinician [12, 13].

HIIT, MICT, and their comparative roles in the chronic inflammatory response

Currently, no studies have directly compared the anti-inflammatory effects of HIIT versus MICT in cancer; however, such comparisons in other clinical populations indicate that HIIT may be more effective. Interleukin-6 (IL-6) is a pleiotropic cytokine with growth properties that promote tumor progression [12, 14]. While not studied in patients with cancer specifically, 12 weeks of HIIT significantly suppressed the plasma levels of IL-6 in patients with heart failure compared to MICT [13]. Another phenomenon that potentiates tumor growth and upregulates inflammation is the overexpression of reactive oxygen species (ROS) generated by persistent inflammatory reactions [15]. HIIT appears to moderate this pathway compared to MICT by increasing glutathione peroxidase (GPx) [16], an enzyme with protective effects against ROS [15] and therapeutic potential for several malignancies [17, 18]. Moreover, chronic expression of pro-inflammatory factors along with ROS facilitates insulin resistance [19] that can further promote tumor progression via increased production of the mitogenic insulin-like growth factors (IGFs) [19]. Meta-analytic evidence supports that insulin resistance is better regulated via HIIT compared to MICT [20] while some of the prevailing HIIT mechanisms responsible for the normalization of insulin activity involve increases in muscle mitochondrial biogenesis and glucose transporter 4 (GLUT4) protein [21]. Collectively, the aforementioned findings favor HIIT over MICT in fostering homeostatic processes that may play a therapeutic role in tumor control via mitigation of systemic and chronic inflammation.

The anti-inflammatory benefits of HIIT are also important for cardioprotection in patients at high risk of treatment-related cardiotoxicity [22]. These benefits are mediated by greater increases in cardiorespiratory fitness and reductions in cardiovascular risk factors in HIIT compared to MICT [7–10]. Moreover, promising evidence supports that HIIT significantly enhances antioxidant status and flow-mediated dilation compared to MICT in patients with heart failure [23]. This likely achieved through increasing production of nitric oxide [23] that has relevance in combatting chemotherapy-induced increases in ROS—one of the primary mechanisms contributing to cardiotoxicity in cancer patients [24]. Collectively, the effect of HIIT on cardiorespiratory fitness, endothelial function, and ROS to prevent or mitigate treatment-related cardiotoxicity is compelling and requires further investigation.

Safety of HIIT for people with cancer

Evidence indicates that HIIT can be safely performed in people with cancer [7, 8, 25–32]. In the ten studies that have conducted HIIT in a total of 522 people with cancer, one serious adverse event was reported (Table 1). In a randomized controlled trial (RCT) of mixed cancer diagnoses undergoing HIIT and resistance training or usual care, Adamsen and colleagues reported a grade 3 seizure following a HIIT session in a participant with brain cancer [26]. The participant was discharged on the same day and the authors suggest that patients with brain tumors or brain metastases should avoid high-intensity training [26]. Two additional nonsevere adverse events following HIIT (symptomatic hypotension) were reported in colorectal survivors in an RCT conducted by Devin et al. [7]. Despite these episodes, both participants completed the study. Midtgaard et al. found that six participants developed lymphedema over 12 months of HIIT and resistance training versus no adverse events in the control group [30]. It is unclear whether these symptoms were attributable to HIIT or resistance training; however, all six participants completed the intervention without additional symptoms [30]. While the current volume of data suggest that HIIT is safe in a variety of cancers, we support recommendations by Adamsen et al. for screening prior to each HIIT session to detect abnormalities and/or respond to fluctuations in health status [26]. This is especially important given that exercising at very high intensities may lead to temporary suppression of specific immune factors [33] that could cause further complications to individuals with abnormal blood parameters and compromised immune system.

Conclusion and recommendations for future research

Accumulating evidence supports that HIIT mitigates inflammation directly or via its effects on oxidative stress and insulin resistance. These effects are of vital importance in oncology given the relationship between inflammation and tumor growth. Moreover, the anti-inflammatory effect of HIIT may help protect against cardiotoxicity associated with several types of cancer treatment that can lead to cardiovascular disease and mortality. The role of HIIT in cancer survivorship will be significantly advanced through investigations of the following key areas. First, there is a need to establish

Table 1 HIIT protocols and potentially attributable adverse effects in cancer survivors

Authors	Sample	HIIT protocol	Adverse effects
Adams et al. [25]	Testicular Cancer HIIT: $n=35$ Control: $n=28$	Frequency: 3x/week Exercise Intensity: 75–95% VO_{2peak} Active recovery/rest intensity: 5–10% below the ventilatory threshold High-intensity training duration: 16 min Active recovery duration: 12 min High-intensity bouts per session: 4 Modality: walking/running Program length: 12 weeks	No adverse effects
*Adamsen et al. [26]	Mixed malignancies HIIT: $n=135$ Control: $n=134$	Frequency: 3x/week Exercise Intensity: 85–95% HRmax Active recovery/rest intensity: N/A High-intensity training duration: N/A Active recovery duration: N/A High-intensity bouts per session: N/A Modality: cycling Program length: 6 weeks	A participant with brain tumor had a grade 3 seizure after training
Devin et al. [7]	Colorectal cancer HIIT: $n=40$ MICT: $n=17$	Frequency: 3x/week Exercise Intensity: 85–95% HRpeak Active recovery/rest intensity: 50–70% HRpeak High-intensity training duration: 16 min Active recovery duration: 12 min High-intensity bouts per session: 4 Modality: cycling Program length: 4 weeks	Two participants experienced symptomatic hypotension after a training session
Hwang et al. [27]	Lung cancer HIIT: ($n=13$) Control: ($n=11$)	Frequency: 3x/week Exercise Intensity: 80% VO_{2peak} Active recovery/rest intensity: 60% VO_{2peak} High-intensity training duration: N/A Active recovery duration: N/A High-intensity bouts per session: N/A Modality: treadmill or cycling ergometer Program length: 8 weeks	No adverse effects
*Kampsoff et al. [28]	Mixed malignancies HIIT: ($n=91$) Low- to moderate-intensity resistance and endurance exercise: ($n=95$) Control: ($n=91$)	Frequency: 2x/week Exercise Intensity: ≥80% HRR Active recovery/rest intensity: N/A High-intensity training duration: 15 min Active recovery duration: 3 min High-intensity bouts per session: 3 Modality: treadmill or cycle ergometer Program length: 12 weeks (7 weeks of HIIT)	No adverse effects
*Licker et al. [29]	Lung cancer HIIT: ($n=74$) Control: ($n=77$)	Frequency: 2–3x/week Exercise Intensity: 80–100% peakWR Active recovery/rest intensity: N/A High-intensity training duration: 10 min Active recovery duration: 10 min High-intensity bouts per session: 40 Modality: cycle ergometer Program length: 3–4 weeks	No severe adverse effects

Table 1 (continued)

Authors	Sample	HIIT protocol	Adverse effects
*Midtgaard et al. [30]	Mixed malignancies HIIT: ($n=108$) Control: (106)	Frequency: 1x/week Exercise Intensity: 90–95% HRmax Active recovery/rest intensity: N/A High-intensity training duration: N/A Active recovery duration: N/A High-intensity bouts per session: N/A Modality: cycle ergometer Program length: 12 weeks	Six participants developed lymphedema
Schmitt et al. [31]	Mixed malignancies HIIT: ($n=13$) Low to moderate intensity: (13)	Frequency: 3x/week Exercise Intensity: ≥95% HRpeak Active recovery/rest intensity: slow walking High-intensity training duration: 8 min Active recovery duration: 16 min High-intensity bouts per session: 8 Modality: treadmill or cycle ergometer Program length: 3 weeks	No adverse effects
*Schulz et al. [32]	Breast cancer HIIT: ($n=15$) Control: ($n=11$)	Frequency: 2x/week Exercise Intensity: 85–100% VO_{2peak} Active recovery/rest intensity: load-less intervals High-intensity training duration: 10 min Active recovery duration: 10 min High-intensity bouts per session: 10 Modality: cycle ergometer Program length: 6 weeks	No adverse effects
Toohey et al. [8]	Mixed malignancies HIIT: ($n=8$) MICT: ($n=8$)	Frequency: 3x/week Exercise Intensity: ≥85 HRmax Active recovery intensity: N/A High-intensity training duration: 3.5 min Active recovery duration: 7 min High-intensity bouts per session: 7 Modality: cycle ergometer or treadmill Program length: 12 weeks	No adverse effects

HRpeak peak heart rate, *HRR* heart rate reserve, *HRmax* maximum heart rate, *VO2peak* peak oxygen uptake, *peakWR* peak work rate, *min* minutes, *secs* seconds, *N/A* not available

*The intervention group underwent HIIT and resistance training

whether HIIT can effectively prevent and/or attenuate persistent inflammatory states in the oncology population given the potency of chronic inflammation on tumor development and progression. Second, HIIT may be an ideal strategy to employ for surgical prehabilitation [29, 34] where maximizing an exercise dose in a short waiting period is essential to achieve peri- and postoperative benefits while potentially controlling disease progression. Third, given potential safety concerns, more research is needed to conclusively determine adverse event rates and risk stratification when employing HIIT in people with cancer.

References

1. Cormie P, Zopf EM, Zhang X, Schmitz KH (2017) The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects. Epidemiol Rev 39(1):71–92. https://doi.org/10.1093/epirev/mxx007
2. Rundqvist H, Augsten M, Strömberg A, Rullman E, Mijwel S, Kharaziha P et al (2013) Effect of acute exercise on prostate cancer cell growth. PLoS ONE 8(7):e67579. https://doi.org/10.1371/journal.pone.0067579
3. Leung P-S, Aronson WJ, Ngo TH, Golding L, Barnard RJ (2004) Exercise alters the IGF axis in vivo and increases p53 protein in prostate tumor cells in vitro. J Appl Physiol 96(2):450–454. https://doi.org/10.1152/japplphysiol.00871.2003
4. Pedersen L, Idorn M, Pedersen BK, Straten P, Hojman P, Pedersen L et al (2016) Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell short article voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent. Cell Metab 23(3):1–9. https://doi.org/10.1016/j.cmet.2016.01.011
5. Courneya KS, Friedenreich CM, Quinney HA, Fields ALA, Jones LW, Fairey AS (2003) A randomized trial of exercise and quality of life in colorectal cancer survivors. Eur J Cancer Care (Engl) 12(4):347–357. https://doi.org/10.1046/j.1365-2354.2003.00437.x

6. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG et al (2009) Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol 27(3):344–351. https://doi.org/10.1200/JCO.2007.15.4963
7. Devin JL, Sax AT, Hughes GI, Jenkins DG, Aitken JF, Chambers SK et al (2016) The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial. J Cancer Surviv 10(3):467–479. https://doi.org/10.1007/s11764-015-0490-7
8. Toohey K, Pumpa KL, Arnolda L, Cooke J, Yip D, Craft PS et al (2016) A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors. PeerJ 4:e2613. https://doi.org/10.7717/peerj.2613
9. Weston KS, Wisloff U, Coombes JS (2014) High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. Br J Sports Med 16:1227–1234. https://doi.org/10.1136/bjsports-2013-092576
10. Milanovic Z, Sporis G, Weston M (2015) Effectiveness of high-intensity interval training (HIT) and continuous endurance training for VO2max improvements: a systematic review and meta-analysis of controlled trials. Sports Med 45(10):1469–1481. https://doi.org/10.1007/s40279-015-0365-0
11. Thompson WR (2015) Worldwide survey of fitness trends for 2016: 10th anniversary edition. ACSM's Heal Fit J 19(6):9–18
12. Grivennikov SI, Karin M (2011) Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. Ann Rheum Dis 70(Suppl 1):i104–i108. https://doi.org/10.1136/ard.2010.140145
13. Fu TC, Wang CH, Lin PS et al (2013) Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. Int J Cardiol 167(1):41–50. https://doi.org/10.1016/j.ijcard.2011.11.086
14. Taniguchi K, Karin M (2014) IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. Semin Immunol 26(1):54–74. https://doi.org/10.1016/j.smim.2014.01.001
15. Liou G-Y, Storz P (2010) Reactive oxygen species in cancer. Free Radical Res. https://doi.org/10.3109/10715761003667554
16. Mitranun W, Deerochanawong C, Tanaka H et al (2014) Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. Scand J Med Sci Sports 24(2):e69–e76. https://doi.org/10.1111/sms.12112
17. Qi X, Ng KT, Lian QZ, Liu XB, Li CX, Geng W et al (2014) Clinical significance and therapeutic value of glutathione peroxidase 3 (GPx3) in hepatocellular carcinoma. Oncotarget 5(22):11103–11120. https://doi.org/10.18632/oncotarget.2549
18. Barrett CW, Ning W, Chen X, Smith JJ, Washington MK, Hill KE et al (2013) Tumor suppressor function of the plasma glutathione peroxidase gpx3 in colitis-associated carcinoma. Cancer Res 73(3):1245–1255. https://doi.org/10.1158/0008-5472.CAN-12-3150
19. Godsland IF (2009) Insulin resistance and hyperinsulinaemia in the development and progression of cancer. Clin Sci (Lond) 118(5):315–332. https://doi.org/10.1042/CS20090399
20. Jelleyman C, Yates T, O'Donovan G et al (2015) The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. Obes Rev 16(11):942–961. https://doi.org/10.1111/obr.12317
21. Hood MS, Little JP, Tarnopolsky MA et al (2011) Low-volume interval training improves muscle oxidative capacity in sedentary adults. Med Sci Sports Exerc 43(10):1849–1856. https://doi.org/10.1249/MSS.0b013e3182199834
22. Pecoraro M, Del Pizzo M, Marzocco S, Sorrentino R, Ciccarelli M, Iaccarino G et al (2016) Inflammatory mediators in a short-time mouse model of doxorubicin-induced cardiotoxicity. Toxicol Appl Pharmacol 293:44–52. https://doi.org/10.1016/j.taap.2016.01.006
23. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM et al (2007) Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 115(24):3086–3094. https://doi.org/10.1161/CIRCULATIONAHA.106.675041
24. Angsutararux P, Luanpitpong S, Issaragrisil S (2015) Chemotherapy-induced cardiotoxicity: overview of the roles of oxidative stress. Oxid Med Cell Longev 2015:795602. https://doi.org/10.1155/2015/795602
25. Adams SC, Delorey DS, Davenport MH, Stickland MK, Fairey AS, North S et al (2017) Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: a phase 2 randomized controlled trial. Cancer. 2017. https://doi.org/10.1002/cncr.30859
26. Adamsen L, Quist M, Andersen C, Moller T, Herrstedt J, Kronborg D et al (2009) Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. BMJ 2009 339:b3410. https://doi.org/10.1136/bmj.b3410
27. Hwang CL, Yu CJ, Shih JY, Yang PC, Wu YT (2012) Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy. Support Care Cancer 20(12):3169–3177. https://doi.org/10.1007/s00520-012-1452-5
28. Kampshoff CS, Chinapaw MJ, Brug J, Twisk JW, Schep G, Nijziel MR et al (2015) Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the resistance and endurance exercise after chemotherapy (REACT) study. BMC Med 13:275. https://doi.org/10.1186/s12916-015-0513-2
29. Licker M, Karenovics W, Diaper J, Frésard I, Triponez F, Ellenberger C et al (2017) Short-term preoperative high-intensity interval training in patients awaiting lung cancer surgery: a randomized controlled trial. J Thorac Oncol 12(2):323–333. https://doi.org/10.1016/j.jtho.2016.09.125
30. Midtgaard J, Christensen JF, Tolver A, Jones LW, Uth J, Rasmussen B et al (2013) Efficacy of multimodal exercise-based rehabilitation on physical activity, cardiorespiratory fitness, and patient-reported outcomes in cancer survivors: a randomized, controlled trial. Ann Oncol 24(9):2267–2273. https://doi.org/10.1093/annonc/mdt185
31. Schmitt J, Lindner N, Reuss-Borst M, Holmberg HC, Sperlich B (2016) A 3-week multimodal intervention involving high-intensity interval training in female cancer survivors: a randomized controlled trial. Physiol Rep. https://doi.org/10.14814/phy2.12693
32. Schulz SV, Laszlo R, Otto S, Prokopchuk D, Schumann U, Ebner F et al (2017) Feasibility and effects of a combined adjuvant high-intensity interval/strength training in breast cancer patients: a single-center pilot study. Disabil Rehabil 21:1–8. https://doi.org/10.1080/09638288.2017.1300688
33. Gleeson M (2007) Immune function in sport and exercise. J Appl Physiol 103:693–699. https://doi.org/10.1152/japplphysiol.00008.2007
34. Weston M, Weston KL, Prentis JM, Snowden CP (2016) High-intensity interval training (HIT) for effective and time-efficient pre-surgical exercise interventions. Perioper Med [Internet] 5(1):2. Available from http://www.perioperativemedicinejournal.com/content/5/1/2