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TOPICAL REVIEW

Benefits beyond cardiometabolic health: the potential of frequent high intensity 'exercise snacks' to improve outcomes for those living with and beyond cancer

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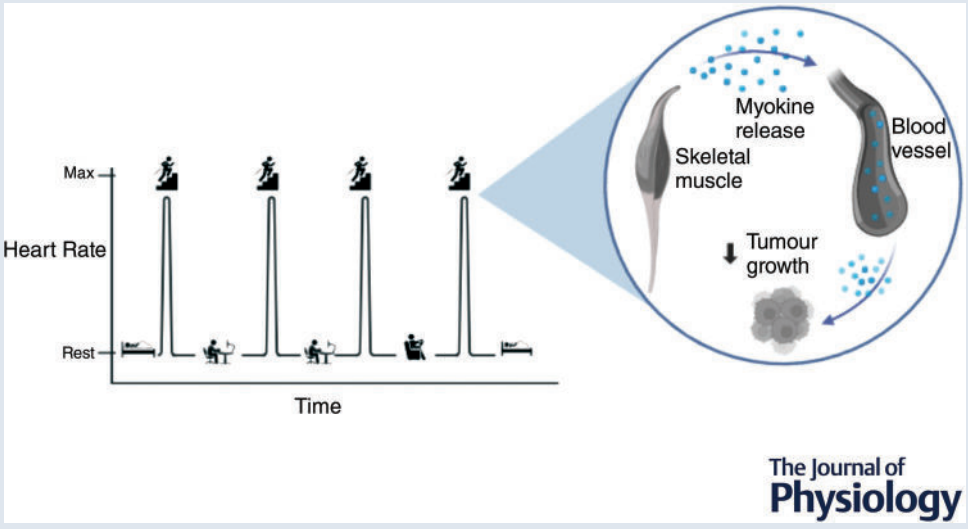

Abstract High intensity interval training (HIIT) has been shown to consistently elicit rapid and significant adaptations in a number of physiological systems, across many different healthy and clinical populations. In addition, there is increasing interest in how some acute, yet transient responses to high intensity exercise potentially reduce the risks of particular diseases. Recent

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work has shown that discrete, brief bouts of high intensity exercise (termed 'exercise snacks') can improve glucose control and vascular health and thus counter the negative cardiometabolic consequences of prolonged, uninterrupted periods of inactivity. In this brief review, we advance the case, using evidence available from pre-clinical studies in the exercise oncology literature, that brief, frequently completed bouts of high intensity exercise embedded within an individual's overall daily and weekly physical activity schedule, may transiently impact the tumour micro-environment and improve the health outcomes for those who have been diagnosed and treated for cancer.

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Abstract figure legend The figure demonstrates the 'exercise snack' hypothesis and how repeated brief bouts of high intensity exercise completed during the course of a day may impact tumour related outcomes. Pre-clinical data show that the transient increases in serum concentrations of myokines in response to exercise can suppress breast, colon and prostate cancer cells growth *in vitro*. There is a strong rationale that the intensity of these exercise bouts should ideally be above the 'anaerobic threshold', so as to recruit the larger skeletal muscle motor units. However, the minimum duration of exercise is not clear; the duration of exercise in those studies that have shown suppression of cancer cell growth following the application of post-exercise serum has been $\geq$16 min. Research is yet to determine whether shorter bouts of high intensity exercise can elicit similar suppression of cancer cell growth. (Created with BioRender.com).

Background

Evidence showing the potency of high intensity interval training (HIIT) to elicit rapid and significant improvements in cardiorespiratory fitness and skeletal muscle oxidative capacity in healthy and athletic populations has led, over the past 15–20 years, to research examining its safety, feasibility and efficacy in clinical populations (Gibala, 2021; Gibala, et al., 2012; Little et al., 2011). An increasing number of studies show that HIIT improves a range of health markers (e.g. cardiometabolic fitness, increased skeletal muscle mass and reduced body fat) in patients with diabetes, non-alcoholic fatty liver disease, advanced cardiovascular disease and heart failure, and in pre-surgery patients, as well as in those who have been diagnosed and treated for breast, colon and prostate cancer (Cassidy et al., 2017; Devin et al., 2016; Hallsworth et al., 2015; Hollekim-Strand et al., 2014; Papadopoulos et al., 2021; Weston et al., 2016; Wisløff et al., 2007). There is also growing evidence that high intensity exercise can elicit transient changes in blood that may reduce the risks of developing cardiovascular disease (Little et al., 2014).

The acute influence of 'exercise snacks' on markers of cardiometabolic health

Compelling epidemiological data show that prolonged periods of inactivity increase the risk of cardiometabolic diseases (Dunstan et al., 2021). Mechanistically, activity- and inactivity-mediated changes in glucose control and vascular function have attracted the particular attention of researchers (Islam et al., 2022; Little et al., 2014). In their recent narrative review, Islam et al. (2022) describe how 'exercise snacks', which they define as discrete $\leq$1-min bouts of vigorous exercise performed periodically throughout the day, can lower blood glucose and insulin concentrations (Rafiei et al., 2021) and temporarily improve arterial haemodynamics (Caldwell et al., 2021). In the present context, exercise snacks can be considered as planned, structured and repetitive bouts of physical activity (Caspersen et al., 1985) rather than more general advice to increase vigorous intermittent lifestyle physical activity (VILPA; Stamatakis et al., 2021). Also, 'vigorous' refers to exercise at intensities $\geq$ 64% of $\dot{V}_{O_2peak}$, $\geq$77% of maximal heart rate and/or eliciting a rating of perceived exertion (RPE) of at least 14 based on the Borg 6–20 scale (Garber et al., 2011; Gibala & Little, 2020). In each of the original studies in Islam et al.'s review, 'exercise snacks' consisted of stair climbing completed 1–4 h apart (Islam et al., 2022). The acute improvements in endothelial function resulting from these exercise snacks have been attributed to increased blood-flow induced shear stress, while the reductions in blood glucose concentrations probably involve non-insulin dependent glucose uptake by the active skeletal muscle (Daugaard & Richter, 2001). Collectively, the findings of Caldwell et al. (2021), Rafiei et al. (2021) and others have the potential to inform and extend recommendations aimed at reducing the negative consequences associated with prolonged sitting in the workplace and, in turn, improving cardiometabolic health over the lifespan.

Exercise training and HIIT in cancer populations

Regular exercise is estimated to reduce the risk of all-cause mortality and cancer-specific mortality by 30%–50% in breast cancer (Holmes et al., 2005), 44%–61% in prostate cancer (Kenfield et al., 2011) and 38%–50% in colorectal cancer (Schmid & Leitzmann, 2014). Suggested physiological mechanisms include decreases in systemic inflammation (Petersen & Pedersen, 2005), reductions in body fat (McTiernan, 2008), decreases in insulin-like growth factor-1, reductions in the circulating concentrations of sex hormones, improved immune function (Dethlefsen, Pedersen et al., 2017; Farley et al., 2022), and/or reduced oxidative stress (Guinan et al., 2013). Within the broader exercise oncology literature, a number of RCT's have examined the influence of HIIT on various health outcomes; the findings from these studies show that HIIT improves cardiorespiratory fitness, quality of life and body composition in a number of different cancer populations and that many of these changes occur in only 4 weeks of training (Devin et al., 2016; Herranz-Gómez et al., 2022). However, in addition to these longer-term benefits that occur with training, there are also acute, transient responses to discrete bouts of exercise that have been shown to temporarily reduce the growth of cancer cells *in vitro*.

The acute anti-tumour benefits of exercise

To compare the influence of resting and post-exercise blood on cancer cell viability, Dethlefsen et al. (2016) sampled serum from breast cancer survivors before and after 2 h of exercise. These samples were then applied to breast cancer cells (MCF-7 and MDA-MB-231) *in vitro*. The authors reported that cancer cell viability was reduced following the application of the post-exercise serum, but not following the resting serum. Similar findings were reported by Devin et al. (2019), who examined the influence of resting and post-exercise serum on the growth of colon cancer cells (CaCo-2 and LoVo) *in vitro*. In their study, blood from colon cancer survivors was sampled at rest and immediately following 4 × 4 min of cycle ergometry at ∼85% $\dot{V}_{O_2peak}$; growth of the colon cancer cells was suppressed, but only when the post-exercise serum was applied. In the same study, the authors found significant increases in IL-6, IL-8 and TNFα concentrations in their post-exercise blood samples (Devin et al., 2019). *In vitro* research with prostate cancer cell lines has yielded comparable results; Rundqvist et al. (2013) found that serum sampled from healthy males following 60 min of cycling at increasing intensities suppressed the growth of LNCaP cells, while more recently, Kim et al. (2022) reported that when compared to resting serum, post-exercise serum sampled from advanced prostate cancer patients significantly suppressed the growth of prostate cancer cells (DU-145) *in vitro*. Exercise in this latter study involved participants completing 34 min of moderate-to-high intensity interval exercise at ∼70%–85% maximum heart rate (MHR).

Macroscopically, acute bouts of exercise can influence the tumour microenvironment via exercise-mediated increases in blood perfusion and by reducing tumour hypoxia (Koelwyn et al., 2017). In addition, evidence suggests that myokines (i.e. cytokines released from active skeletal muscle) affect the tumour microenvironment. A number of post-exercise blood-borne myokines, including oncostatin M (OSM), secreted protein acidic rich in cysteine (SPARC), irisin and decorin, have been implicated in suppressing the growth of cancer cell lines (Kim et al., 2021). Also associated is the exercise-mediated mobilisation of IL-6 sensitive NK cells that occurs in response to increases in systemic adrenalin concentrations during exercise (Pedersen et al., 2016). Indeed, Dethlefsen, Hansen et al. (2017) have shown that the acute catecholamine response to exercise is particularly important in facilitating the suppression of cancer cell growth. Using pre-clinical experimental models, this group has shown that blockade of β-adrenergic signalling can completely blunt exercise-mediated reductions in cell viability and tumour formation (Dethlefsen, Hansen et al., 2017).

Research is yet to determine how intense and for how long an exercise bout needs to be for the necessary changes in serum to be elicited that will suppress the growth of cancer cells *in vitro*. In the pre-clinical studies reviewed above, exercise has ranged from 16 min of HIIT (Devin et al., 2019) through to 2 h of resistance exercise and high intensity 'spin' cycling (Dethlefsen et al., 2016). Whether intense 'exercise snacks' (<60 s), similar to those that have been shown to improve glucose control and vascular function, could also suppress the growth of cancer cells is not yet clear. Nonetheless, it is reasonable to suggest that exercise, irrespective of the duration, will ideally need to be above the intensity that corresponds to an individual's anaerobic threshold, which is the intensity above which there is a significant increase in the contribution of anaerobic metabolism to the energy yield. Though this is yet to be experimentally tested, exercise involving the larger motor units, such as the case at more intense levels of exercise, will favour a greater production of myokines compared to lower-intensity exercise. The recruitment of the Type IIb motor units at exercise intensities above the anaerobic threshold will also be accompanied by a greater production and release of adrenalin and noradrenalin (Sales et al., 2019), and therefore, the mobilisation of NK cells would probably be higher (Dethlefsen, Hansen et al. 2017). Shah et al. (2019); Pedersen et al., 2016 have reported rapid increases in catecholamine release at exercise intensities above the ventilatory threshold, with catecholamine concentrations being positively correlated

with exercise stages of increased power. Finally, the exercise will need to involve large muscle groups, so as to engage the highest possible number of contracting fibres and ensure a high net production and release of myokines into circulation.

In addition to determining the optimal intensity and minimum duration of exercise that will potentially suppress cancer cell growth, the frequency of exercise is also an important variable to consider. The limited available pre-clinical evidence shows that the anti-tumour effect resulting from exercise is transient. Devin et al. (2019) found that compared to serum sampled immediately post-exercise, serum sampled 120 min following their high intensity interval exercise had no influence on the growth of colon cancer cell lines. And in their study that showed reduced growth of cancer cells with serum sampled immediately post-exercise, Kim et al. (2022) reported that the increases in the serum concentrations of OSM, IL-6, SPARC and IL-15 that occurred in response to exercise, had returned to baseline within 30 min following exercise. Thus, once exercise stops and skeletal muscle is no longer contracting, production and release of myokines also ceases. As homeostasis is restored and the myokines are removed from circulation, any potential cancer-suppressing influence diminishes. The importance of this is communicated in the title of the paper by Dethlefsen, Pedersen et al. (2017): 'Every exercise bout matters: linking systemic exercise responses to breast cancer control'. *Frequency* of exercise therefore becomes important to take full advantage of the transient tumour suppressing effects of exercise. Indeed, it is entirely likely that the cumulative exposure to these transient acute effects of exercise is responsible for many of the improved outcomes in physically active cancer survivors. The 'exercise snack' hypothesis extends this framework to suggest that accumulating repetitive bouts of brief but sufficiently intense activity throughout a day could augment the potential cancer suppressive effects of regular exercise programmes by maximising the frequency of exposure to these transient post-exercise effects.

Future directions

A number of different lines of research are needed to build on the pre-clinical findings reviewed here and to test whether exercise snacks can be tolerated and should be recommended for those who have been diagnosed and treated for cancer. First, acute serum

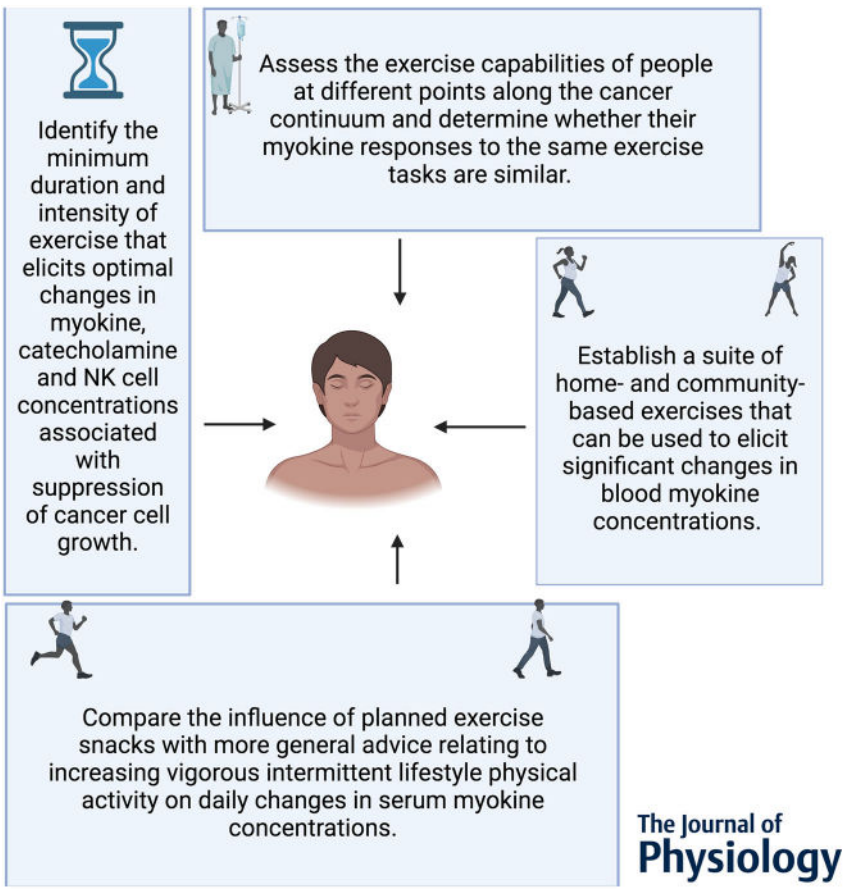

Figure 1. Directions for future research
Summarised are some directions for future research that will address current gaps in the literature and test whether exercise snacks should be recommended for those who have been diagnosed and treated for cancer. (Created with BioRender.com).

myokine, catecholamine and NK cell responses across different exercise interventions need to be compared. This will help identify a minimum intensity and duration of exercise that can elicit the changes in serum that have been associated with reduced cancer cell growth. Second, assessing the exercise capabilities and myokine responses with people at different points along the 'cancer continuum' i.e. before treatment, during treatment and following treatment, to brief bouts of vigorous exercise will inform the development of exercise recommendations. Third, different types of exercise snacks (e.g. home and community-based activities) that can each elicit significant increases in myokine concentrations need to be identified and tested by exercise physiologists to determine whether they can be tolerated and adopted. This is necessary for the pre-clinical and laboratory work to be translated to real-world settings. Finally, comparing the physiological responses to exercise snacks (i.e. planned, structured and repetitive physical activity) with more general, unstructured increases in daily physical activity, will establish whether exercise prescription in the current context is necessary – or whether those living with and beyond cancer need to simply increase their daily activity levels to gain the benefits from exercise-mediated myokine release. These directions for future research are summarised in Fig. 1.

Conclusion

Pre-clinical findings in the exercise oncology literature relating to the acute tumour suppressing effects of blood-borne factors suggest that brief, high intensity bouts of exercise may provide protection against cancer cell growth. Whether the prescription of 'exercise snacks' will be appropriate for this population will depend on future research that identifies the minimum duration and optimal intensity of exercise necessary to elicit the temporary excursions in systemic, circulating biomarkers (e.g. myokines) in serum that are associated with the tumour suppression, and determining whether this form of exercise is tolerated and acceptable for people living with cancer. Finally, it is important to highlight that we are not advocating that 'exercise snacks' or frequent, brief bouts of vigorous exercise replace all other exercise activities that enable individuals to meet the current physical activity guidelines. Rather, the potential value will come from having these exercise bouts embedded within an individual exercise programme and contributing to overall daily physical activity levels.

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Additional information

Competing interests

None declared.

Author contributions

D.G.J. conceived the initial outline for the article, with input from J.L.D., K.L.W., J.G.J., and T.L.S. All authors contributed equally to the drafting of the manuscript, all authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship and only those who qualify for authorship are listed.

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