EXERCISE

Exercise as medicine for survivors of paediatric cancer

Marit Hjorth and Mark A. Febbraio

Evidence suggests that physical activity is beneficial for patients with and survivors of cancer. A recent study found that vigorous exercise was associated with reduced mortality in paediatric cancer survivors. Here we discuss these findings in the context of potential mechanisms mediating some of the health effects of exercise in cancer.

Refers to Scott, J. M. et al. Association of exercise with mortality in adult survivors of childhood cancer. *JAMA Oncol.* https://doi.org/10.1001/jamaoncol.2018.2254 (2018).

The Childhood Cancer Survivor Study (CCSS) is a large study that was created in 1994 to gain more knowledge on long-term effects of paediatric cancer and cancer therapy[1]. More than 35,000 individuals who had survived childhood cancer for more than 5 years after diagnosis were retrospectively recruited from 31 centres across the USA and Canada. Participants were diagnosed between 1970 and 1999; hence, the CCSS cohort comprises 30 years of childhood cancer survivors. After inclusion, the participants were followed up for several years to assess long-term health outcomes. A recent analysis of data from the CCSS found that vigorous exercise was associated with reduced mortality decades after the initial cancer diagnosis, indicating that physical activity has long-term benefits for survivors of paediatric cancer.

> “circulating factors that are altered during exercise could influence tumour cell growth directly”

With advances in cancer treatment regimes, the 5-year survival for paediatric cancers is >80%. Notwithstanding, the risk of morbidity and mortality is drastically increased in survivors of childhood cancer for decades after the initial diagnosis[2]. While recurrence or progression of the primary disease is a major contributor to mortality at early time points after diagnosis, the excess mortality at late time points is largely due to late complications of cancer therapy. For instance, survivors of childhood cancer are at high risk of developing subsequent malignant neoplasms (that is, malignancies not related to the original cancer).

Recently, Jessica M. Scott and colleagues[1] analysed data from the CCSS to examine the association between vigorous physical activity and mortality in adults who had survived paediatric cancer. The amount of vigorous exercise was measured via questionnaire at baseline ($n = 15{,}450$) and at median 10 years follow-up, in a subset of participants ($n = 5{,}689$). Overall, exercise was associated with reduced incidence of all-cause mortality. The participants who reported no vigorous exercise at baseline of the study had the highest risk of mortality with a cumulative incidence rate of 11.7% after 15 years. After adjusting for clinical covariates, the risk of death was reduced by ~20% in all other quartiles of exercise (compared with no exercise), meaning that there was a lack of a dose–response relationship, and that even a small amount of exercise was associated with reduced mortality.

Furthermore, vigorous exercise was, to some extent, associated with reduced risk of subsequent neoplasms. The participants who maintained a high activity level at both baseline and follow-up had a 55% reduction in risk ($P = 0.049$). A similar risk reduction was observed in the participants who had an activity level of 15–18 metabolic equivalent of task (MET) hours per week (equivalent to ~2.5 hours of jogging per week), which was the activity level that gave the largest reduction in all-cause mortality. This association was not significant when analysing risk in quartiles of activity, and there was no dose–response relationship. The findings, however, are encouraging and consistent with data from observational studies on adult-onset cancers; physical activity after diagnosis is associated with reduced all-cause mortality and recurrence for breast, colon and prostate cancer[3]. Although results are variable, the reported reduction in mortality is frequently reported to be ~40–50%. Physical activity is also associated with a reduction in risk of developing several types of cancer, with the strongest evidence for cancers of the colon, breast and endometrium[4]. So far, no randomized clinical trials have investigated the long-term effects of exercise on morbidity and mortality, and this study by Scott and colleagues[1] is, to our knowledge, the first observational study on the association between exercise and mortality in survivors of childhood cancer.

It is impossible to generalize the reported effects of exercise to encompass all patients with cancer or individuals who have survived cancer. The effects of exercise before or after a cancer diagnosis are clearly dependent on the patient, cancer type, tumour somatic mutations and histology. In many types of cancer, however, exercise has been reported to improve aspects of general health as well as disease-related and treatment-related adverse effects. In addition, regular and acute exercise has been shown to have antitumorigenic effects. The antitumorigenic effects of exercise could be of importance to patients with childhood cancer or survivors of childhood cancer who are at risk of recurrence or subsequent neoplasms.

> “the reported associations between exercise and morbidity and mortality … are encouraging”

Physical activity clearly has numerous health benefits for the general public, which would also be relevant to many patients with cancer or individuals who have survived cancer. In addition, several short-term

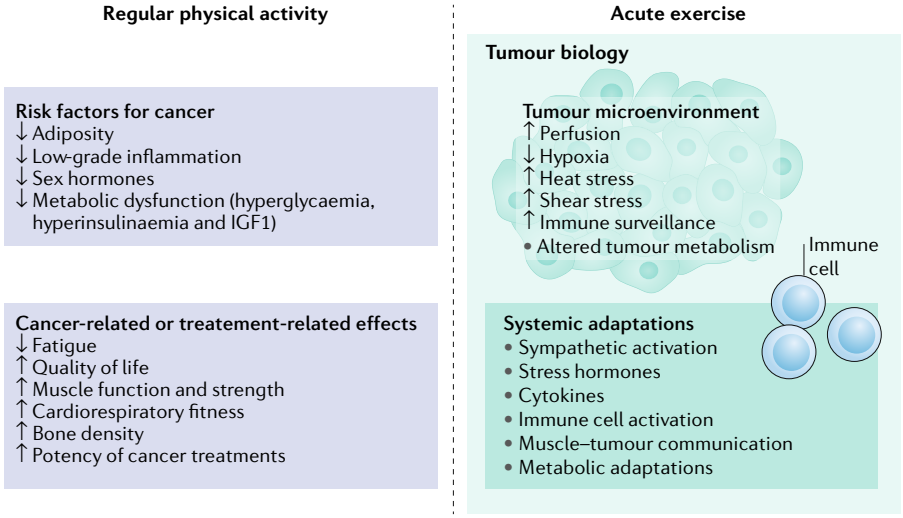

Fig. 1 | **Potential effects of exercise in cancer prevention, progression or treatment.** Physical exercise has antitumorigenic effects that might be of importance to patients with cancer and individuals who have survived cancer but are at risk of recurrence or subsequent neoplasms. Regular physical activity might reduce the risk of developing cancer by improving cancer risk factors including obesity, low-grade inflammation and metabolic dysfunction (such as hyperglycaemia and hyperinsulinaemia). An acute bout of exercise leads to systemic adaptations that might impair tumour progression. Some of these adaptations are: increased blood flow, which might lead to increased tumour perfusion and oxygen delivery; systemic metabolic adaptations and altered tumour metabolism; activation of the immune system and intra-tumoural immune cell infiltration; increased secretion of catecholamines, which are important for immune activation, but can also regulate tumour suppressor pathways; and muscle–tumour crosstalk via myokines. IGF1, insulin-like growth factor 1.

clinical intervention studies on patients with paediatric and adult cancer have shown benefits of exercise on disease-related and treatment-related adverse effects[3,5], including improvements in cardiorespiratory fitness, muscle strength, fatigue and health-related quality of life.

The antitumorigenic effects of exercise (FIG. 1) are probably mediated by many different mechanisms[6]. Regular physical activity might protect against tumour development by modulating cancer risk factors. For instance, physical activity protects against obesity and low-grade inflammation and improves metabolic homeostasis. Physical activity, via reduced adiposity, can also lead to lower levels of oestrogen, which is of importance to the development of breast cancer.

Interestingly, an acute bout of exercise leads to systemic adaptations that can have direct effects on tumour biology. Exercise is accompanied by increased blood flow, perfusion of the tumour and metabolic alterations that can influence tumour progression. Another example is activation of the immune system and immune cell mobilization, which can increase cancer cell cytotoxicity. In a seminal, preclinical study by Line Pedersen and colleagues[7], voluntary wheel running reduced tumour growth or incidence by ~60% in five different mouse models of cancer. The suppression of tumour development could be attributed to exercise-induced redistribution of cytotoxic natural killer cells to the tumour, which was dependent on adrenaline and IL-6.

Furthermore, circulating factors that are altered during exercise could influence tumour cell growth directly. For instance, breast cancer cell lines incubated with serum from an acute exercise session had reduced viability in vitro, and pre-incubation with the same serum resulted in slower tumour growth after inoculation in mice[8]. This was attributed to exercise-induced secretion of catecholamines and signalling via the Hippo signalling pathway. Circulating factors mediating muscle–tumour crosstalk might also be of importance. Myokines are peptides or proteins secreted from skeletal muscle with either local or endocrine functions[9]. The expression of many myokines is induced by exercise, and some could have antitumorigenic effects. The most well-characterized myokine is IL-6. As previously mentioned, IL-6 was involved in immune cell mobilization during exercise. Skeletal muscle is also able to release extracellular vesicles, which contain more than 5,000 proteins, into the circulation during exercise[10], but it is still unknown whether these can mediate muscle–tumour communication.

Although the data from the CCSS cohort and other observational studies don't provide causal evidence, the reported associations between exercise and morbidity and mortality in patients with cancer and individuals who have survived cancer are encouraging. Collectively, there is now enough evidence from short-term clinical studies, observational and preclinical studies to incorporate physical activity in the management of patients with paediatric cancer and adults who have survived paediatric cancer.

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Competing interests
The authors declare no competing interests.