While there is a large list of EDCs to examine, typically human exposure to these compounds is low relative to the doses used in experimental laboratory studies. As Kioumourtzoglou and colleagues note, however, humans are exposed to a number of environmental chemicals simultaneously across the lifespan and the cumulative effect of low-level EDC exposures could adversely affect inter-generational health.1 For instance, several phthalates — chemicals used in some polyvinyl chloride plastics, personal care products, food processing and pharmaceuticals — have anti-androgenic effects on the developing male fetus, and cumulative phthalate exposure reduces testosterone production in a concentration addition manner. Therefore, cumulative exposure to multiple phthalates could be at levels sufficient to produce multi-generational adverse health effects.

While there has been justifiable emphasis on the health effects of prenatal EDC exposures, it will be important for future studies to consider whether and how paternal EDC exposures affect human health. A growing number of animal studies and a limited number of epidemiological studies show that paternal environmental exposures before conception, including EDC exposures, can influence the health of offspring. One study reported that the offspring and grand-offspring born to fathers who were conditioned to fear the scent of acetophenone had increased sensitivity to acetophenone, despite never having smelled the compound. In F0 males and F1 offspring, these effects were accompanied by hypomethylation of the Olfr151 gene in sperm, which is an olfactory receptor of acetophenone. Recent research by our group has shown that paternal phthalate exposures before conception can affect offspring birthweight and behaviour, sometimes in a sex-specific manner.8,9 Given the potential for some paternal preconception exposures to affect sperm epigenetic information and offspring phenotypes, we need to determine whether these changes are associated with the health of subsequent generations.

If studies demonstrate that environmental exposures before conception affect the risk of disease in subsequent generations, then we will need to consider this period of susceptibility in environmental chemical and pharmaceutical regulations. Specifically, this means considering not only the exquisite sensitivity fetus, infant and child in such regulations, but also the developing gametes. For clinicians, it would be prudent to advise patients to avoid or reduce exposures to EDCs, when possible, before trying to become pregnant; however, for the health of an individual’s grandchildren, it is not clear whether avoiding exposures to EDCs would only need to be during the periconceptional or prenatal period or for an extended period before conception. New studies that include repeated measurements of EDC exposures before conception and during pregnancy, detailed assessments of offspring health and biomarkers of epigenetic mechanisms will help us to address this question and to develop public health interventions that can improve the health of not only our children, but possibly our grandchildren and great-grandchildren.

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**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.


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. 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.

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.1 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 neoplasms (that is, malignancies not related to the original cancer).

Recently, Jessica M. Scott and colleagues 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 and follow-up had a 55% 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. 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. 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 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.

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

The antitumorigenic effects of exercise are probably mediated by many different mechanisms. 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, 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. 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. 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, 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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New horizons for osteoanabolic treatment?
Anita Ignatius* and Jan Tuckermann*

Novel osteoanabolic strategies are highly desired to treat osteoporotic bone loss or augment fracture repair in patients at risk of healing complications, including individuals with osteoporosis or inflammatory disorders. Whereas current osteoanabolics address osteoblast function, research by Ren Xu and colleagues highlights the skeletal endothelium as a promising target to promote bone formation.