follow-up periods and clear documentation of treatment exposure duration are also needed to capture onset of outcomes, which might manifest only after a long period of exposure. Future studies should also ensure that temporality is well documented, whereby patients being assessed for risk of malignancy after therapy with topical calcineurin inhibitors should be free of incident lymphoma at commencement to avoid confounding by indication.

The comprehensive coverage of existing studies and detailed sensitivity analyses performed by Devasenapathy and colleagues provide added reassurance that the risk of malignancy with topical calcineurin inhibitors is likely to be no higher than the background risk in the general population.[9] This should in turn assure physicians and patients of the continued safety of topical calcineurin inhibitors in the management of atopic dermatitis. This, and other well designed studies, should empower health-care providers and stakeholders to strengthen the push for regulatory authorities to remove the black-box warning, which has inadvertently impeded optimal patient care.

I declare no competing interests.

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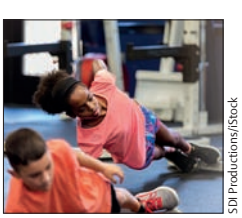
Childhood cancer: exercise is medicine

Advances in the management of childhood cancer have provided meaningful improvements in clinical prognosis. These improvements have led to an increase in the number of survivors, who often have post-treatment complications that can cause adverse health outcomes later in life. Sequelae associated with cancer treatment (chemotherapy and radiotherapy) can lead to harmful and often persistent changes in the developmental process, in the cardiopulmonary (eg, cardiotoxicity and impaired ventricular function years after treatment) and metabolic (eg, dyslipidaemia) systems, and in body composition (excess abdominal adiposity coupled with muscle weakness and poor bone health; appendix).[1] The physical ability of survivors of childhood cancer is often impaired and daily life activities can be challenging.[2]

Health promotion interventions are needed to reduce cancer-associated morbidity and promote good health practices while patients transition to survivorship. Several studies have addressed the effects of physical exercise on physical capacity and cancer-related outcomes along the childhood cancer journey, including in very young patients (aged 4–7 years) or during the most aggressive phases of treatment (eg, hospitalisation for haematopoietic stem-cell transplantation).[3] Such interventions were typically aerobic activities (eg, running or cycling), sometimes in combination with muscle-strengthening tasks such as weight lifting. Meta-analytical evidence shows that, especially when supervised, exercise interventions during or after treatment are safe and improve physical capacity,[4] functional mobility during daily life activities,[2] muscle strength, physical activity levels, body-mass index, and fatigue.[5] Exercise interventions also have a cardioprotective effect by improving—or attenuating the decline of—cardiovascular function associated with treatment.[4]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Published **Online**
October 26, 2022
https://doi.org/10.1016/S2352-4642(22)00306-6

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However, another major concern for survivors of childhood cancer (especially, but not limited to, those treated for brain tumours) is risk of cognitive dysfunction, with subsequent impairment in academic achievement, social behaviour, and vocational performance in adulthood. In *The Lancet Child & Adolescent Health*, Joshua D K Bernal and colleagues[6] assessed the effects of physical activity and exercise interventions on cognitive function in individuals affected by childhood cancer. In their topical meta-analysis, the authors included randomised controlled trials (RCTs) and non-randomised studies that compared the effects of physical activity with no intervention or usual care in 1277 individuals (median age 12 (IQR 11–14) years; 674 [52·8%] male and 603 [47·2%] female) who had finished treatment for a median of 2·5 (IQR –1·1 to 3·0) years. The results provided moderate-quality evidence that physical activity improved cognitive performance measures and patient-reported indicators of cognitive function, with only nine mild adverse events reported.

Bernal and colleagues[6] provide evidence that the benefits of exercise are largely multisystemic, thereby also affecting cognitive function. A growing number of studies indicate that myriad molecules known as exerkines are released during exercise; these exerkines include not only muscle-derived factors (known as myokines) but also factors from other tissues, and these molecules can reach different target tissues in which they exert numerous beneficial effects (eg, anti-inflammatory action, improved insulin sensitivity, or lipolysis), including the CNS.[7] One exerkine is brain-derived neurotrophic factor and its exercise-mediated release contributes to neurogenesis (even in adults), cognition, mood, and synaptic plasticity.[7]

Consistent with previous data,[2–5] the findings of Bernal and colleagues[6] support the benefits of physical exercise in managing childhood cancer and its late effects. There is strong evidence that exercise is an effective coadjuvant treatment to minimise the side-effects of cancer treatment in adults, with international experts endorsing that "people living with and beyond cancer should be as active as is possible for them".[8] Childhood cancer should not be an exception to such proactive recommendations, especially in light of widespread physical inactivity that starts early in life.[9] Indeed, WHO recommends that children and adolescents living with disability do at least an hour of moderate-to-vigorous intensity (mostly aerobic) physical activity each day, with more intense tasks (including muscle and bone strengthening activities, such as lifting weights) incorporated on 3 or more days per week, while reducing the amount of time spent being sedentary (eg, recreational screen time).

Higher quality evidence and large multicentre RCTs with long-term follow-up are needed to address the scalability of exercise interventions in the context of childhood cancer. Additional studies should focus specifically on adolescents with cancer, a population that must cope with major challenges during a complex period of their life. It also remains to be determined whether, beyond attenuating treatment toxicities, exercise has the ability—as in adult malignancies, partly through improved immunosurveillance[10]—to exert direct anti-tumoural effects in younger populations with immature immunity (especially innate immunity), potentially attenuating the risk of childhood tumour recurrence.

For more on **WHO physical activity recommendations** see https://www.who.int/news-room/fact-sheets/detail/physical-activity

We declare no competing interests. Research by AL and CF-L is funded by the Wereld Kanker Onderzoek Fonds as part of the World Cancer Research Fund International grant programme.

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