Physical exercise—A toxin-free complement to cancer therapy

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Funding information
The author was funded by a project that was listed by the Free State of Thuringia under the number 2019 FGR 0083 and co-financed by funds from the European Union within the framework of the Social Fund (ESF), Grant/Award Number: FKZ: 2019 FGR 0083

Cancer is a heterogeneous disease which can influence many facets of the human physiology. Treatments and therapies of cancer are as diverse as the illness itself and often come with toxic side effects. In many reviews, researchers regularly summarize the newest results and try to untangle the complexity of cancer and cancer-related research. This review aims to connect recent research on the field of molecular biology of cancer with recent results from exercise physiology that were published in Acta Physiologica.

A sedentary lifestyle as it is led by modern society nowadays is a leading cause of diseases and disabilities. Physical activity and exercise are described as a potential prevention against a diversity of chronic conditions, including cancer. Exercise training was brought into focus lately as a toxin-free addition to promote a positive outcome of cancer treatments (surgery, chemo-, radiation-, hormonal therapy). Even Drosophila melanogaster was recruited as a new model for exercise research in order to enable large scale studies with broad sets of parameters. Physical exercise can counteract many cancer promoting factors, such as high inflammatory levels, high levels of adipose tissue, cachexia, cardiovascular diseases and a low mitochondrial capacity. Therefore, researchers are more and more eager to understand the molecular mechanisms that promote the manifold of effects that exercise can have on our physiology.

1 IMMUNE RESPONSE

The immune system plays a critical role when it comes to fighting cancer, as it recognizes and attacks non-native cells. Immunotherapy drugs are supposed to support the immune response. But physical exercise has also been shown to influence composition and activity of the innate immune system. A clinical study including 12 older healthy adults describes changes in the physiology of skeletal muscle macrophages following changes in their physical activity. William Evans discusses the possibility, that elevated blood flow-induced shear stress - ie due to exercise - may play a role in the recruitment of natural killer cells, which can target and kill cancerous cells. Bigley and his team had a group of 16 cyclists performing 30-min exercises at different lactate levels/intensities and took blood samples before, during and after practice. The samples 1h post-exercise were enriched of cytotoxic natural killer cell subsets. This means that exercise possibly influences not only the number of NK cells, but also their cytotoxicity.

2 LYMPHEDEMA

When surgical therapy includes the removal of lymph nodes, patients often suffer from a high risk for lymphedema. A systematic review on the effects of exercise on cancer-related...
lymphedema concludes, that resistance exercise training produces significant gain in muscular strength without provoking cancer-related lymphedema. Kwan confirms this outcome in another systematic review, stating that exercise of varying modalities is not associated with the development or exacerbation of breast cancer-related lymphedema and can be safely pursued with proper supervision. Another systematic review, which included 11 randomized controlled trials on women with breast cancer in aftercare even suggests that exercise can improve breast cancer related lymphedema parameters. Overall, even though studies differ in their conclusions if lymphedema symptoms can be reduced by physical exercises, they do come to the agreement, that under supervision it is safe for patients to engage in physical activities.

3 | CANCER CACHEXIA RELATED MUSCLE WASTING

Low skeletal muscle mass is associated with poor clinical outcomes especially in older patients. Looijard et al give a review regarding possible pathophysiological mechanisms behind this phenomenon. These mechanisms include systems similar to those that are supposed to be influenced by physical exercise, such as the inflammatory system, insulin-glucose metabolism, energy regulation of mitochondria and the body’s reaction to potentially aggressive cancer drugs. They propose physical exercise or exercise mimetics – the application of substances such as mitochondrial dysfunction seems to be one key player.

MUSCLE WASTING

The regulation of reactive oxygen species (ROS) and their roles as messengers and in oxidative stress is a complex topic itself. A certain level of mitochondrial respiration is necessary to ensure a healthy antioxidant defense in the cell, which again is an important anti-cancer propagation mechanism. Hubackova et al, give a review on the impact of oxidative phosphorylation (OXPHOS) on mitochondria-induced cell death of cancer versus senescent cells. One difference that they emphasize between proliferating and non-proliferating cells is their level of respiration. The increase in OXPHOS-generated ROS in proliferative tumor cells cannot properly be cleared, due to low rates of respiration. Such a reduction of respiration also might promote invasiveness and other physiologies of cancer.

A brief overview of the main signals that facilitate changes in maximal oxygen uptake of the human body ($V_{O2\max}$) due to endurance training is given by Lundby and Montero. Several groups described that exercise training can alter mitochondrial function. Cardinale et al elucidate the role of mitochondria in muscle oxidative capacity. Larsen et al examined the respiratory system of mitochondria isolated from the Vastus lateralis and Triceps brachii in 12 healthy volunteers and found that mitochondrial affinity for oxygen increased after a series of highly intensive sprint interval trainings. Axelrod et al found that a 12 weeks supervised aerobic program lead to changes in mitochondrial fusion and fission proteins, which promotes a more fused, tubular network and can contribute to improvements in substrate utilization after exercise. In addition, Arribat et al found that mitochondria from Vastus lateralis did adapt to high energy demands of a new exercise routine: 22 healthy, previously sedentary participants followed 4 months of supervised endurance exercise. Post-intervention mitochondrial content increased; so did biogenesis and fusion. Among other effects, OXPHOS capacity and $O_2$ turnover increased. Fiorenza’s group describes changes in the expression of markers of mitochondrial turnover, anti-oxidant protection and oxidative damage in Vastus lateralis after 6 weeks of high intensity interval training.

This review only gives an impression of the diversity of physical exercise research and its possibilities to develop cancer treatment-complementing therapies based on physical exercise. Especially in former sedentary patients, a shift towards a more active lifestyle can support their immune system during its fight against cancer. A physical exercise therapy could counteract muscle wasting and alter mitochondrial physiology.

CONFLICT OF INTEREST

The author declares no financial or other conflict of interest that might bias this article.

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How to cite this article: Groeneveld K. ExActa: Physical exercise—A toxin-free complement to cancer therapy. Acta Physiol. 2021;231:e13606. https://doi.org/10.1111/apha.13606