

EXERCISE - A SYNERGISTIC MEDICINE IN CANCER MANAGEMENT

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Exercise is now being recognised as a critical synergistic medicine in the management of all cancers. In fact, current international guidelines from such leading authorities as the American Cancer Society now include a very clear and strong statement. Cancer patients should be physically active on most if not every day regardless of the type of cancer, stage or even when undergoing difficult treatments.

Exercise is a sub-category of physical activity which is planned, structured, repetitive and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness and health (capacity, structure, function, homeostasis) is the objective. “Exercise medicine” is the physical assessment and prescription of exercise specifically for the prevention or treatment of injury or illness. Analogous to pharmaceutical interventions through the use of exogenous medicine, specific exercise drives endogenous “medicine” as it results in extensive systemic changes in body biochemistry in particular hormones and cytokines released by various organ systems including skeletal muscle during exercise and recovery. There is also direct structural adaptation and repair, and blood perfusion and vascular adaptations which are highly beneficial to patients with cancer. It is also now establish that targeted exercise medicine facilitates other therapies such as radiation and chemotherapy while ameliorating treatment side-effects side-effects.

Exercise has an important role throughout the cancer control framework. Pre-diagnosis exercise has been proven to reduce risk of many cancers in particular colon, breast, prostate and lung cancer. Being physically active and of normal body fat levels improves the accuracy of cancer screening leading to earlier detection and thus better patient outcomes. Once diagnosed with cancer, exercise is being implemented pre-treatment to increase the fitness and improve body composition and patient resilience leading up to surgery, chemo therapy or radiation therapy. During treatment phases appropriate exercise reduces toxicities and side-effects while facilitating the effectiveness in particular for chemotherapy and radiation therapy. Following completion of cancer treatment exercise is critical for rehabilitation of the patient to reduce fatigue, regain muscle mass and limit fat gain. It has

also been established that exercise reduces the risk of cancer recurrence. Four patients at the end stage of life exercise is important for maintaining quality of life and physical function up to the point of death.

The current international recommendations for exercise for people with cancer is to complete 75 to 150 minutes per week of vigorous to moderate aerobic exercise and two or more resistance (strength) training sessions each week. While this generic recommendation would provide considerable improvement in patient outcome, clearly more targeted exercise medicine prescriptions would achieve even greater benefit in terms of reduced morbidity, improved quality of life and enhance survival. For example, 150 minutes per week of walking will have no beneficial effect on the osteoporosis and sarcopenia associated with various hormone treatments for cancer. Similarly, it is likely counter-productive for a cancer patient with severe cachexia to be encouraged to pursue an aerobic exercise program which will only exacerbate the energy imbalance and lead to further tissue loss. For such a patient highly specific anabolic resistance training in combination with nutritional support is the recommended prescription.

An increasing quality and quantity of retrospective and observational studies are demonstrating highly meaningful survival benefits for people with cancer if they maintain a certain volume and intensity of physical activity. For example, Kenfield et al¹ reported 61% lower risk of prostate cancer specific death in men who performed more than three hours per week of vigorous activity. What must now be demonstrated is the survival advantage that can be achieved through targeted exercise medicine specifically prescribed to address the cancer type, stage of disease, treatment side effects and comorbidities. Our hypothesis is that the relative rate of mortality will be even lower for those patients who undertake tailored exercise medicine. INTERVAL – MCRPC is a multicentre, randomised, controlled phase 3 trial² evaluating highly specific anabolic and aerobic exercise prescription tailored for men with metastatic castrate-resistant prostate cancer with the primary outcome being overall survival. The second research priority is to determine the specific mechanisms by which certain exercise modalities and dosages actually impact tumour biology. To date the majority of research exploring this avenue has been conducted in animal or in-vitro models and demonstrating quite astounding and complex effects directly on tumour tissue and individual cancer cells. For example, Rundqvist et al³ exposed prostate cancer cells in-vitro to human serum drawn post 60 minutes of cycling exercise and reported 31% inhibition of cell growth.

Pedersen et al⁴ reported exercise to suppress tumour growth through NK cell mobilization and tumour infiltration in rodents.

Potential mechanisms currently being explored include⁵:

- 1) Modulation of circulating factors including both hormones and cytokines (e.g. insulin, sex-steroid hormones, myokines and adipokines).
- 2) Improved immune function through increased cell surveillance, activation, and infiltration by the innate system.
- 3) Proliferation of hormone receptors in non-tumour tissues reducing bioavailability for cancer cells.
- 4) Reduced systemic inflammation and oxidative stress.
- 5) Increased tumour blood perfusion enhancing immune system effectiveness as well as chemotherapy delivery and DNA damage through radiation therapy.
- 6) Epigenetic modulation of gene expression and telomere alterations and telomerase activity.
- 7) Platelet cloaking of circulating tumour cells.
- 8) Hyperthermia resulting from exercise sufficient to induce tumour cell apoptosis.

The pursuit of understanding of these mechanisms combined with existing knowledge of exercise benefits for associated comorbidities is critical for more effective and efficient prescription of exercise medicine for cancer management. Further, there is the potential for the development of novel molecules for delivery of exogenous medicine to treat cancer or enhance the effects of exercise. The potential of exercise as a medicine for cancer management working independently and synergistically with other therapies is considerable and must be incorporated into standard care of people with cancer.

References

1. Kenfield et al: Journal of Clinical Oncology, 29:726-32, 2011
2. Saad, Newton et al: American Society for Clinical Oncology, Chicago, June 3-7, 2016, 2016
3. Rundqvist et al: PLoS One 8:e67579, 2013
4. Pedersen et al: Cell Metab 23:554-62, 2016
5. Galvao, Newton et al: Nat Rev Urol, 10.1038/nrurol.2016.46, 2016