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Novel Therapies

Review

Exercise for cancer survivors: A review

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Abstract

Introduction

As survivorship becomes increasingly common with marked improvements in the detection and treatment of cancer, the deleterious effects of the disease and its treatment need continued attention. Exercise is developing a valuable role in the cancer-rehabilitation process. Over the past two decades, a substantial amount of research has been done on the effects of exercise for cancer survivors. The aim of this review was to provide an overview of some of the psychological and physical benefits of exercise and to explore exercise-induced immune function specific to cancer survivors.

Discussion

It is commonly accepted that physical activity may improve various physical and psychosocial factors in cancer survivors while potentially reducing the rate of recurrence and improving overall survival. Exercise of low-to-moderate intensity is reportedly a feasible and safe option to mediate the effects of medical treatment and may have the ability to attenuate the loss in physical performance typically associated with cancer treatment. Most research in this area is specific to breast and prostate cancer, although recent literature is focusing on other tumour types. Of recent interest is the immunological response of exercise in cancer survivors, both on and off treatment. The cytokine cascade in response to exercise differs from that induced by infection, which leads to the question of how exercise impacts those who are immunocompromised. Although inflammation is linked with the process of tumourigenesis and exercise has been linked with decreased inflammation, surprisingly few studies have examined the immunological impact of exercise within the cancer population.

Conclusion

Physical activity has been found to produce beneficial health-related outcomes for cancer survivors, but exercise dose response is still being explored. Further research is needed to clearly identify the immune response to exercise as experienced by cancer survivors.

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Introduction

Treatment outcomes for many cancers continue to improve with an increasing cohort of long-term disease-free survivors. However, late effects of treatment may impact upon patients' short- and long-term physical and psychosocial health[1,2]. Treatment-related symptoms can last for months or even years post-treatment and may impact upon overall health of the survivor.

Cancer patients are often prescribed drugs to help minimize side effects of chemotherapy and related treatment, but drug therapy is viewed as a short-term solution that only temporarily resolves debilitating side effects[3]. Some of the most debilitating physical symptoms associated with treatment are fatigue, anaemia, muscle wasting, reduced balance and coordination[4]. These physical symptoms can bring about diminished energy and physical performance that may reduce overall mood state and quality of life (QoL)[4,5]. Cognitive functioning may also be impaired after chemotherapy treatment; patients reported having trouble focusing, reading and driving[5]. Increasing levels of physical activity may improve various physical[6–8] and psychosocial factors in cancer survivors[6,9], while positively impacting the rate of recurrence and overall survival[8,10,11]. Research suggests that low-to-moderate intensity exercise is a feasible and safe option to mediate the effects of medical treatment[3,4,12]. Endurance exercise training may have the ability to attenuate the loss in physical performance typically associated with cancer treatment[13,14].

Exercise is developing a valuable role in the cancer-rehabilitation process[15]. A review of quantitative data from 82 controlled trials of physical activity interventions for cancer survivors found that exercise was well tolerated both during and after treatment (without adverse events)[16]. This supports the conclusion from a recent American College of Sports Medicine (ACSM) roundtable that exercise training is safe during and after cancer treatment and may result in enhanced physical functioning, QoL and reduced cancer-related fatigue (CRF) in several cancer survivor groups[17,18]. The aim of the current review was to outline some of the psychological and physical benefits and explore the potential impact of exercise on immune function in cancer survivors.

Discussion

Morbidity

A variety of medical complications are often found to be a direct consequence of cancer treatment and

FOR CITATION PURPOSES: *Daroux-Cole L, Pettengell R, Jewell A.* Exercise for cancer survivors: A review. OA Cancer 2013 May 20;1(1):5

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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negatively affect the QoL in cancer survivors. Cancer-related treatments increase the risk of secondary tumours and affect other systems such as cardiac, pulmonary, endocrine and immunologic functions[8]. Cancer patients may be prone to secondary malignancies, obesity and cardiovascular diseases (CVDs), all of which are known causes of late-term morbidity and mortality[19,20]. Evidence suggests death from CVD and diabetes occurs at a higher rate in cancer survivors than in the general population[20,21].

Exercise has been found to reduce the risk of cancer recurrence and mortality for some cancer survivors[10,22], as well as decrease CVD risk factors by lowering resting blood pressure[23] and resting heart rate[24] markers of systemic inflammation, specifically C-reactive protein (CRP)[25] and tumour necrosis factor-alpha (TNF-α)[26]. Regular exercise offers protection against all-cause mortality[26]. Emerging observational and clinical data signify the importance of physical activity in solid tumour patients and provide increasing evidence that exercise positively impacts major clinical endpoints such as rate of infection, rate of recurrence and overall survival[8,10,11,22].

Psychosocial impact of exercise

The psychosocial consequences of a diagnosis and treatment of malignant disease are significant and often protracted. In one study, 22% of malignant patients fulfilled the criteria for psychiatric illness[27]. Many studies have found decreased overall QoL, physical function and increased anxiety and depression amongst cancer survivors when compared with their premorbid measures and with healthy adults[28]. Perceptions of how cancer has affected survivors' lives may be related to one's functional abilities and QoL[29]. Exercise can promote adaptation to the many stressors of cancer and related treatment both during and after therapy[30] whilst enhancing one's capacity to resume normal lifestyle activities including employment and hobbies, resulting in improved QoL, greater independence and sense of control.

Quality of Life (QoL)

Exercise has a positive effect on a broad range of QoL dimensions in cancer patients[31]. Appropriately designed exercise interventions are generally associated with positive QoL outcomes in cancer survivors[30,32]. Exercise is associated with higher QoL and overall life satisfaction scores amongst breast cancer patients on treatment[33]. A meta-analysis reported better QoL in cancer survivors who exercised compared with those who did not: these results were consistent amongst different tumour types (breast, colorectal and gynaecologic cancer and lymphoma)[30]. Another recent meta-analysis showed that the significant positive impact of exercise on QoL (when compared with control groups and with their baseline levels of QoL) was still present at follow-up[32]. Interestingly, exercise dose emerged as an important moderator of QoL; interventions of longer duration and higher aerobic metabolic equivalents (METs) produced greater change in QoL[32].

Health-related QoL (HRQL), a subcomponent of QoL, has become an integral part of exercise intervention evaluation as patient perception of the benefits of exercise can have a substantial effect on coping and treatment effectiveness[34]. Research has shown that PA is positively associated with HRQL across several cancer groups[35,36].

Overall Mood Disturbance

Mood disturbance is common amongst people with cancer[37]. High mood disturbance is associated with increasing symptoms[38] and negatively impacts upon functional status and QoL[39]. Exercise decreases mood disturbance amongst cancer survivors[40]; even walking has shown an improvement (minimum 90 min, 3 times per week)[41].

Anxiety and Depression

Anxiety and depression afflict 20–50% of cancer patients[42,43]; severity fluctuates depending on the type of cancer, stage of cancer, treatment choice as well as stress and coping strategies of the patient[44]. With regular exercise, cancer survivors experience a reduction in depression and anxiety, thus positively impacting QoL[31,45]. Sessions lasting 30 plus minutes in duration for no more than 12 weeks resulted in the largest anxiety improvements, although even acute exercise has shown a reduction in anxiety levels[41,44,46,47].

Depression is estimated to be four times higher in cancer patients than in general population[48]; 58% of cancer patients experience symptoms of depression[49]. Patients and survivors often experience depressive mood immediately upon diagnosis[50], which may persist long after treatment has finished[51]. The response to exercise has often been positive, thereby resulting in a decrease in depressive symptoms[52], although a number of studies show no change (although no adverse effects have been reported)[53,54].

Fatigue

A common side effect of cancer treatment is fatigue[55], which continues long after the completion of treatment in up to 75% of cancer survivors[56]. Chronic fatigue is often associated with lower levels of physical activity amongst cancer survivors (specifically within the first 5 years after treatment)[57].

CRF is one of the most debilitating and distressing side effects of cancer and treatment[58,59]. Exercise is useful in reducing CRF[18,60], as inactivity contributes to fatigue[61]. Aerobic exercise is effective at reducing fatigue during[41,52,62], and after treatment[15,63,64]. More specifically, aerobic exercise of moderate intensity shows a strong

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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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trend towards reducing chronic fatigue in cancer patients[41,65,66]. In a recent systematic review, survivors of several types of cancer who took part in exercise interventions had reduced CRF levels when compared with their usual care (the greatest reduction was seen amongst exercising older patients)[67].

The impact of resistance training on CRF has been recently examined (amongst men with prostate cancer[68]. Although both resistance and aerobic exercise reduced fatigue in the short term, resistance exercise generated longer term fatigue reduction (as well as improved QoL and physical strength)[68]. CRF levels improve in direct proportion to the intensity of resistance exercise performed[67]. Amongst cancer patients with persistent CRF, a combination of endurance (30-min walking) and resistance/coordination exercises performed weekdays for 3 weeks resulted in significant improvements in mental and physical fatigue scores[54].

Transitioning from 'patient to survivor'

It is commonly accepted that there may be disrupted adjustment at different times during the survivorship experience[69]. The transition period from the completion of treatment to re-entry into one's 'normal' lifestyle is often burdened with disruption, uncertainty and distress[70–72]. Once treatment finishes, patients have more time to deal with the psychological struggles of the cancer journey as well as any existing issues from before cancer diagnosis[71,72]. Fifty-three percent of survivors reported that their emotional needs were harder to cope with than physical needs during the transition period[73], suggesting that this time may be particularly important to one's cancer recovery as it impacts the cancer survivors' experience of stress, which may exacerbate late effects[73]. Exercise has been shown to reduce stress and provide many psychological benefits to cancer survivors[17,74].

Physiological effects of exercise training

It is widely accepted that regular physical activity protects against a number of physiological disorders including numerous cancers and has been found to enhance health, longevity and well-being beyond the effectiveness of medical treatment[75]. Improved heart and lung function, skeletal muscle function, improved body composition, increased life expectancy, increased bone mass density and whole-body metabolism are seen with regular exercise; the protective effect of exercise occurs through improved glucose uptake and insulin sensitivity[76], lowered blood pressure[77], decreased resting heart rate[24] and improved blood lipid profile[75]. Adaptation to exercise starts immediately (even with acute exercise), progresses with continued exposure and is specific to both training stimuli and genetic make-up[78].

Physical Efficiency

Due to the deleterious effects of cancer and its treatment, patients often experience a loss of physical capacity. Both chemotherapy and radiotherapy appear to have a negative impact on the cardiorespiratory system[79] and muscular function[80]. Patients are often unable to maintain their pre-disease level of physical activity and functioning and report reduced physical and role functioning due to physical conditions[81]. Resulting muscle atrophy and cardiopulmonary toxicities make physical exercise taxing; decreased oxygen uptake can make regular daily activities feel very challenging[82].

Improvements in aerobic capacity have been observed with exercise, amongst both patients undergoing treatment and those who have completed treatment[16,83,84]. Functional ability, the measure of an individual's capability to perform everyday activities, is rated as the most important, yet least possessed dimension of QoL amongst cancer survivors[85]. By making daily tasks easier to perform, aerobic capacity positively impacts functional ability. Various types of exercise interventions, including walking, running, home-based activity, strength, stretching and aerobic programmes, have resulted in improved functional ability, aerobic capacity or physical functioning amongst cancer patients and survivors[41,52,86,87]. Research findings indicate that both aerobic capacity and ensuing functional ability improve with regular participation in physical activity.

Muscle Wasting

Skeletal muscle is important for physical function, immune function and metabolic regulation and is responsible for a large portion of glucose metabolism. Skeletal muscle wasting, a common side effect of cancer treatment[88] is often present (to some degree) at the time of diagnosis, but is more prevalent with advanced malignancies[89]. Unfortunately, muscle wasting brings reduced functional ability and weakness[90,91] and negatively affects responsiveness to treatment (increasing morbidity and mortality)[92]. It is also suggested that muscle atrophy during cancer may play a significant role in the development of metabolic syndrome[93].

Resistance training may reduce skeletal muscle wasting (specific to cancer) and stimulate growth in muscle strength and mass[88]; muscular strength gains are common amongst exercising cancer patients and survivors[16]. In prostate cancer patients for example, resistance training alone has resulted in increased muscle mass, reduced treatment-related side effects[94] and increased muscle strength[68,94]. Improved QoL[9] and physical performance scores also resulted from resistance training amongst this group[94].

Weight Maintenance

A number of studies have focused on adiposity in cancer

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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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and survivorship[95–98], as body composition changes are common amongst cancer patients[97,99,100]. Weight gain is an adverse effect of treatment for many cancer types[97] and has been associated with an increased risk for recurrence and death[101–103] (approximately 30–50% of breast cancer deaths among postmenopausal women can be attributed to being overweight)[104]. Despite strong evidence of the statistically and clinically significant associations between low levels of activity and obesity, and cancer recurrence and death, sedentary lifestyle and obesity remain prevalent amongst cancer survivors[103–106]. Obesity is associated with insulin resistance in breast[107] and prostate cancer patients[95,96].

Immune Function and Exercise Training

As stated in the '2011 Position Statement, Immune Function and Exercise (part one)', acute and chronic exercise affect immune production and function[108]. It is suggested that the protective effect of exercise may be due, in part, to the anti-inflammatory effect of regular exercise mediated by cytokine production and release (creating an anti-inflammatory environment) and/or decreased adiposity. Research shows that participants who are sedentary are more susceptible to infection and disease than are their healthy counterparts, suggesting physical activity enhances immune function[109–111].

Cancer is associated with chronic low-grade systemic inflammation[26]; regular exercise produces a long-term anti-inflammatory effect. Regular physical activity is inversely related to serum concentration of inflammatory markers[112], has been found to reduce CRP[25] and suppress TNF-α production, thereby defending against TNF- α-induced insulin resistance (low-grade systemic inflammation is linked with insulin resistance)[26,113].

The mechanism behind the anti-inflammatory effect of exercise is not fully understood, but it is generally accepted that it results from both acute and chronic exercise[110]. It is hypothesised that physical activity causes an increase in the systemic levels of some cytokines with anti-inflammatory properties[110,114]. Skeletal muscle, recently been identified as an endocrine organ, produces and releases cytokines (myokines) upon contraction[115]. During exercise, the level of circulating IL-6 largely increases (up to 100-fold), IL-10 increases, and levels of circulating cytokine inhibitors (such as IL-1ra and sTNF-R) marginally increase. The release of TNF-α and CRP is also impacted by exercise.

IL-6 has been referred to as an 'inflammatory-responsive' cytokine because it does not directly induce inflammation with exercise[116]. Exercise-induced increases in IL-6 have been found to decrease plasma TNF-α, thus decreasing inflammation by blocking the production of TNF-α[26,117]. Muscle-derived IL-6 can decrease the production of TNF-α and IL-1 β and therefore may be responsible for the beneficial effects of exercise on CRF[110]. The normal response to infection is an increase in proinflammatory cytokines, TNF-*α* and IL-1β, but these seem not to increase with exercise, indicating that the cytokine cascade caused by exercise differs from that induced by infection (refer to Figure 1)[26,118].

Both cancer and its treatment (chemotherapy, surgery and radiotherapy) elevate the level of proinflammatory cytokines (TNF-α, IL-1 and IL-6)[119]. Although inflammation is linked with the process of tumourigenesis[120] and exercise has been linked with decreased inflammation, surprisingly few studies have examined the immunological impact of exercise within the cancer population, specifically in terms of inflammation reduction and anti-tumour immunity[108]. The effect of exercise on tumour progression was examined in a mouse model of breast cancer; the reduction in tumour progression was associated with IL-6, monocyte chemoattractant protein (MCP-1) and spleen weight[121]. Further research is needed to suggest a relationship between exercise and tumour progression in humans.

The '2011 Position Statement, Immune Function and Exercise (part one)' reports that the biological mechanisms relating exercise and cancer are not clearly understood

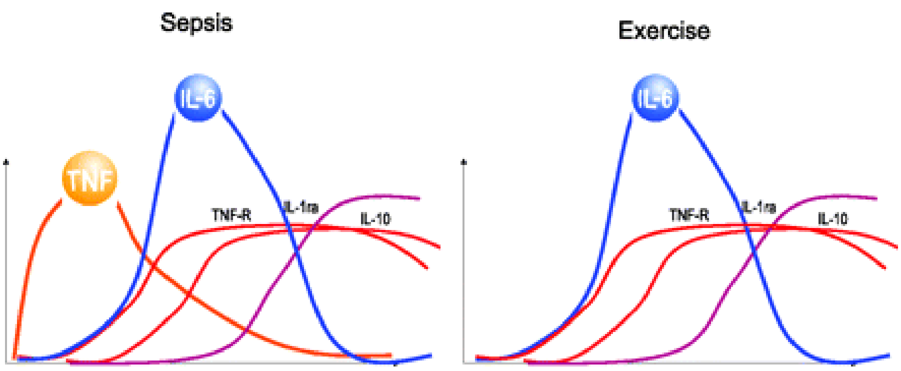

Figure 1: Comparison of sepsis-induced verses exercise-induced increases in circulating cytokines. During sepsis, there is a steep increase in circulating TNF-α, which is followed by an increase in interleukin (IL)-6. In contrast, during exercise, the marked increase in IL-6 is not preceded by elevated TNF-α. From *Pedersen & Febbraio (2008)* with permission from the American Physiological Society (licence 3116880987934).

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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and suggest that the impact specific to tumour type is even less clear[108]. To date, '*no studies have examined the role of exercise in minimizing the immunosuppressive environment that is created by the presence of the tumour*' (2011 Position Statement, Immune Function and Exercise: part one[108]). It is suggested that if the anti-tumour protection offered by exercise occurs, the results should be evident in immune-mediated diseases such as lymphomas[108]. The appropriate exercise dose needed to bring about enhanced immunity is still unknown. It has been proposed that immunity responds in an 'inverted J' format: As exercise intensity increases, immunity improves but only to a point; immunity begins to decline if exercise is too intense, suggesting that exhaustive exercise may suppress immune function and increase susceptibility to disease[122]. Further research is needed to substantiate these findings.

Conclusion

As survivorship becomes increasingly common with marked improvements in the detection and treatment of cancer, the deleterious effects of the disease and its treatment need continued attention. Treatment-induced psychological and physical impairment along with the increased risk of secondary malignancies and CVDs substantiate the need for holistic health interventions specific to this population. Physical activity has been found to produce beneficial health-related outcomes for cancer survivors, but the exact dose response is still being explored.

Abbreviations list

ACSM, American College of Sports Medicine; CRF, cancer-related fatigue; CRP, C-reactive protein; CVD, cardiovascular disease; HRQL, Health-related quality of life; MCP, monocyte chemoattractant protein; MET, metabolic equivalent; QoL, quality of life; TNF-α, tumour necrosis factor-alpha

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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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For citation purposes: *Daroux-Cole L, Pettengell R, Jewell A.* Exercise for cancer survivors: A review. OA Cancer 2013 May 20;1(1):5

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.