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Review Article

Physical activity after cancer: An evidence review of the international literature

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Abstract
The importance of physical activity during and after cancer treatments is now being appreciated, as emerging evidence suggests that it improves several common side-effects of cancer treatments, as well as correlating with improving overall survival and reduced the probability of relapse. The biological mechanisms through which these benefits are achieved may include effects on cell growth regulatory pathways, levels of hormones, gene expression patterns and tumour immunity. Here we review the evidence for the benefits of exercise during and after cancer, discuss the possible underlying biological mechanisms, and suggest ways in which this knowledge may be used to improve mainstream care of cancer patients.
Keywords: Exercise, cancer, survival, side effects

Introduction

The number of individuals surviving cancer is expected to rise by one-third according to estimates from the American Cancer Society and the National Cancer Institute[1]. This means that in the UK over 3 million individuals, and in the USA over 18 million individuals, will be living with the consequences of cancer by 2,022. The increase in the number of survivors is attributed to earlier diagnosis, an aging population, better cure rates and more effective systemic therapies to keep patients with metastatic disease alive for longer. To achieve these benefits, patients often have to endure more complex and arduous therapies, frequently leaving them beleaguered with acute and long-term adverse effects. In addition to being unpleasant, these adverse effects result in financial implications for patients and their families, as well as resulting in a greater usage of health resources.

Although the importance of exercise is beginning to be recognised by health professionals, advocacy groups and charities, it still remains an under-utilised resource. This article highlights the evidence that a physically active lifestyle and formal exercise programmes can help relieve many of the common concerns and adverse effects which plague individuals in the cancer survivorship period.

Physical activity improves well-being after cancer

Dozens of interventional studies have tested the feasibility and potential benefits of exercise in cancer survivors[2,3,4]. Recent meta-analyses of randomised trials involving exercise interventions after cancer, encouragingly demonstrate that the benefits of exercise spanned across several common cancer types and following a range of treatments including surgery, radiotherapy, chemotherapy, hormones and even the newer biological therapies. The most recent meta-analysis of 34 randomised trials published in the BMJ in 2012 involving patients exercising after cancer, demonstrated a benefit for a number of troublesome symptoms particularly fatigue, mood, anxiety and depression; muscle power, hand grip, exercise capacity and quality of life[5].

The American College of Sports Medicine also published a comprehensive review of exercise intervention studies in cancer populations which included data from 85 RCT's of exercise in cancer survivors. Evidence consistently demonstrated that exercise could be performed safely in adjuvant and post-treatment settings. Exercise led to significant improvements in aerobic fitness; increased flexibility and strength; quality of life; anxiety and depression; fatigue, body image, size and composition[4].

The individual categories of symptoms which commonly afflict cancer survivors are now discussed in more detail:

Cancer related fatigue (CRF) is one of the most distressing symptoms experienced by patients during and after their anti-cancer therapies. It is reported by 60-96% of patients during chemotherapy, radiotherapy or after surgery, and by up to 40% of patients taking long-term therapies such as hormonal or biological therapies[6]. The first step to treating CRF is to correct, if possible, any medical conditions that may aggravate it, such as anaemia, electrolyte imbalance, liver failure and nocturia; or to eliminate drugs such as opiates, anti-histamines and anti-sickness medication[7]. The role of exercise was reviewed in 28 randomised, controlled trials (RCTs) involving 2083

participants in a variety of exercise programmes and showed that exercise improved CRF, although the benefit overall was small[8]. A second review of 18 RCTs involving 1,109 participants, sub-divided the data into types of exercise and demonstrated that supervised exercise programmes had the most impact on CRF[9]. Further meta-analyses and reviews have also showed that supervised exercise programmes had better results, with a greater reduction in CRF amongst breast cancer survivors assigned to exercise programmes compared to home-based programmes[4,5,8,10].

Psychological distress, including anxiety and depression, is common after cancer with reported prevalence rates of 25-30%[11]. Patients with psychological distress have also been shown to have reduced survival compared to those who are psychologically healthy[12]. Exercise may help alleviate this symptom and improve mood, as a number of observational studies have shown that cancer patients who exercise have reduced levels of depression and anxiety, better self-esteem and are happier, especially if they involve group activities[13]. The recent meta-analyses of RCTs also demonstrated a reduction in anxiety and depression among individuals assigned to exercise programmes[4,5].

Quality of life (QOL) is lower in many cancer sufferers and survivors, linked to other physical and psychological symptoms of cancer and its' treatment. Meta-analyses of studies of exercise intervention programmes have demonstrated an improvement of QOL at all stages of the illness for the common cancer types and following several types of treatment[4,5]. For example, in a study involving 1,966 patients with colorectal cancer, patients achieving at least 150 minutes of physical activity per week had an 18% higher QOL score than those who reported no physical activity, as measured by the QOL FACT-C[14]. Another study showed similar benefits for breast cancer survivors who had completed surgery, radiotherapy or chemotherapy, and also demonstrated that change in peak oxygen consumption correlated with change in overall QOL[15].

Weight gain:45% of women with breast cancer report significant weight gain[16], and in a study of 440 prostate cancer survivors, 53% were overweight or obese[17]. For patients with bowel cancer, the CALBG 8980 trial showed that 35% of patients post-chemotherapy were overweight (BMI 25.0–29.9), and 34% were obese (BMI 30.0–34.9) or very obese (BMI >35)[16]. The reasons for this are multifactorial, but may include other symptoms of cancer treatment such as fatigue and nausea, causing patients to stop exercising. Regardless of the reasons for weight gain, numerous reviews and a comprehensive meta-analysis of the published literature have demonstrated that individuals who gain weight after cancer treatments have worse survival and more complications[18]. Fortunately, supervised exercise programmes have been shown to reduce weight and have significant other benefits on body constitution and fitness, such as improved lean mass indices, bone mineral density, cardiopulmonary function, muscle strength and walking distance[18,19].

Bone mineral density (BMD): Pre-menopausal women who have had breast cancer treatment are at increased risk of osteoporosis, caused by reduced levels of oestrogen brought on by a premature menopause due to chemotherapy, surgery or hormones. Men who receive hormone deprivation therapy for prostate cancer are also at an increased risk of developing osteoporosis. Accelerated bone loss has also been reported for many other cancers, including testicular, thyroid, gastric and CNS cancers, as well as non-Hodgkin's lymphoma and various haematological malignant diseases[20,21]. Lifestyle factors linked to an increase in the risk for developing osteoporosis include a low calcium and vitamin D intake, a diet low in plant-based protein, lack of physical activity, smoking and excessive alcohol intake[22]. A number of studies have linked regular physical activity with a reduction in the risk of bone mineral loss. Sixty six women with breast cancer were randomized to a control group or an exercise programme. The rate of decline of BMD was -6.23% in the control group, -4.92% in the resistance exercise group, and -0.76% in the aerobic exercise group. The statistically significant benefit was even greater in pre-menopausal women[23]. In another RCT of 223 women with breast cancer, it was found that exercise, over 30 minutes 4-7 times a week, helped preserve bone mineral density even when bisphosphonates (risedronate), calcium and vitamin D had already been prescribed[24].

Thromboembolism: Those with pelvic involvement, recent surgery and immobility, previous history of varicose veins or thrombosis or receiving chemotherapy, are at higher risk[25]. Although strategies such as compression stockings, warfarin and low molecular weight heparin are essential, early mobilisation and exercise remains a practical additional aid in reducing this life-threatening complication[18,26].

Constipation caused by immobility, opiate analgesics or anti-emetics during chemotherapy is a significant patient concern. Exercise reduces bowel transit time, and ameliorates constipation and its' associated abdominal cramps[26].

Physical activity improves survival and reduces relapse

In addition to improving the side effects of treatment for cancer, regular physical activity during and after cancer appears to improve overall survival and reduces the probability of relapse. One of the most convincing studies was an RCT in which 2,437 post-menopausal women with early breast cancer

were randomised to nutritional and exercise counselling, or no counselling, as part of routine follow-ups[19]. In the group receiving counselling, fewer women relapsed and overall survival was greater in the oestrogen-negative subgroup. In another RCT, men with early prostate cancer were randomised to an exercise and lifestyle intervention or standard active surveillance. The average PSA in the intervention group went down, whilst in the control group it went up[27]. This supports a previous RCT of which the primary end point evaluated a salicylate-based food supplement, but it required men in both arms to receive exercise and lifestyle counselling. Although there was no difference in the primary end point, 34% of men, who's prostate specific antigen (PSA) was climbing before trial entry, stabilized[28].

The majority of the other published evidence for a reduced relapse rate and improved survival after cancer originates from retrospective analysis or prospective cohort studies. The National Cancer Institute, in a recent meta-analysis, reviewed 45 of these observational studies. The strongest evidence was demonstrated for breast cancer survivors; the next strongest evidence was for colorectal cancer survivors, followed by prostate cancer[10]. The most notable are summarised below:

Breast cancer: The five most prominent prospective cohort studies (in aggregate more than 15,000 women), have examined the relationship between physical activity cancer and prognosis:

- Irwin et al. (2008)[29] investigated a cohort of 933 breast cancer survivors and found that those who consistently exercised for >2.5 hours per week had a 67% lower risk of all deaths compared to sedentary women.
- Holmes et al. (2005)[30] performed a separate evaluation of 2,987 women in the Nurses' Health Study and found that women walking >3 hours a week had lower recurrence rates, and better overall survival.
- Holick et al. (2008)[31] performed a prospective observational study of 4,482 breast cancer survivors, and found that women who were physically active for >2.8 hours per week had a 35-49% lower risk of dying from breast cancer.
- Pierce et al. (2007)[32] found that the benefits of 3 hours of exercise were even greater if combined with a healthy diet.
- Sternfeld et al. (2009)[33] in the LACE study, evaluated 1,870 women within 39 months of diagnosis. There was a significant difference in overall death rate between the highest and lowest quartile of exercise levels.

Colorectal cancer: The scientific community eagerly awaits the results of the CHALLENGE RCT mentioned above, but a number of retrospective analyses of randomised chemotherapy and cohort trials have been published:

- Haydon et al. (2006)[34]retrospectively analysed a RCT involving patients with stage III bowel cancer and found a significant association between exercise and a 31% reduction in relapse rate.
- Giles et al. (2002)[35]found that of 526 patients recruited into the Australian Cohort Study, those participating in recreational sport 1-2 days per week had a 5 year overall survival of 71%, as opposed to 57% in non exercisers.
- Meyerhardt et al. (2006)[16] found in an analysis of the Intergroup CALGB study, that physically active patients with bowel cancer had 35% reduction in relapse rate in after chemotherapy.
- Meyerhardt et al. (2009)[36] analysed 668 patients with colorectal cancer within the Health Professionals Study. Men who exercised >27 vs. < 3METS-hours / week had a lower cancer-specific mortality.

Prostate cancer: Three cohort studies have demonstrated a survival benefit for physically active men with prostate cancer:

- Kenfield et al. (2011)[37]performed a subset analysis of 2,686 men with prostate cancer, within the Health Professional Study, who exercised >30minutes per week or ≥3 MET-hours of total activity, had a 35% lower risk of overall death, and men who walked at a brisk pace for ≥90 minutes had a 51% lower risk of overall death.
- Richman et al. (2011)[38] reported that 1,455 men with prostate cancer, walking more than 3 hours a week, correlated with an improved survival but only if >3miles/hour.
- Giavannucci (2005)[39], within a prospective analysis, reported that men who exercised vigorously had a lower risk for fatal prostate cancer, although this effect was only seen for men over the age of 65.

Quantity and type of exercise recommended for cancer patients

For reduced cancer relapse and improved well-being, most of the cohort studies summarized above suggest moderate exercise of around 2.5 to 3 hours a week for breast cancer survivors. However, for prostate cancer survivors, mortality continues to decrease if the patient walks 4 or more hours per week, and more vigorous activity is also associated with significant further reductions in risk for all-cause mortality[37]. When the mode of exercise is primarily walking, a pace of at least 3 miles/hour (for >3 hours/week) is recommended for a reduced risk of relapse [38]. Therefore, both the pace and duration of exercise affect the survival benefit achievable from exercise, with more vigorous activity generally having a greater benefit (see Table 1). The best results appear to be with programmes including a combination of aerobic and resistance exercises, particularly within a social group.

Table 1: Summary of exercise guidelines for cancer survivors

• Exercising for >3 hours/week has proven benefits for cancer survival
• A pace of at least 3 miles/hour when walking provides greater benefit than a slower pace
• For optimal benefit, exercise should consist of a combination of resistance and aerobic exercises
• Supervised exercise programmes have shown greater benefits for cancer survivors than home-based programmes

The precise amount of exercise has to be determined on an individual basis and depends on pre-treatment ability, current disability caused by the cancer itself or the treatment, as well as time proximity to major treatments. An exercise programme supervised by a trained professional has major advantages, as they can design a regimen which starts slowly and gradually builds up to an acceptable and enjoyable pace. In addition, they can help motivate the individual to continue exercising for the short and the long-term, and they can judge the optimal exercise levels to improve fatigue, and not aggravate it.

The underlying mechanisms of the potential anti-cancer effects of exercise

The body's chemical environment significantly changes after exercise, best demonstrated in the Ornish study, which found that serum from prostate cancer patients who exercised, had an almost eight times greater inhibitory effect on the growth of cultured androgen dependent prostate cancer cells compared to serum from patients in the control group[27]. The precise chemical mechanism, which the anti-cancer effect remains incompletely understood, but one of the most likely mechanisms involving growth factors such as insulin-like growth factor (IGF-1) and its' binding proteins insulin-like growth factor binding proteins (IGFBPs), due to the central role of these proteins in the regulation of cell growth (see Table 2). After binding to its receptor tyrosine kinase, IGF-1 activates several signalling pathways including the AKT pathway, leading to the inhibition of apoptosis and the promotion of cell growth and angiogenesis[34,40,41]. An inverse relationship of cancer risk with IGFBP3 levels has also been shown, although this effect has not been confirmed in all studies[42]. Exercise has been shown to increase the levels of IGFBP3, and this was associated with a 48% reduction of cancer-specific deaths in a large prospective cohort study of 41,528 participants[43]. Decreased levels for IGF-1 in physically active patients have been reported with an associated survival benefit[44].

Table 2: Summary of the potential biochemical pathways of the anticancer effects of exercise

Class of Effector Molecule	Effector Molecule	Effects of Exercise on Effector Molecule
Cell growth regulators	IGF1	Decreased levels
	IGFBP3	Increased levels
Proteins involved in DNA damage repair	BRCA1	Increased expression
	BRCA2	Increased expression
Regulator of apoptosis and cell cycle arrest	p53	Enhanced activity
Hormones	Oestrogen	Decreased levels
	Vasoactive intestinal protein (VIP)	Decreased levels
	Leptin	Decreased levels (indirect)
Immune system components	NK cells	Enhanced activity
	Monocyte function	Enhanced activity
	Circulating granulocytes	Increased proportion

Exercise has also been shown to have a large impact on gene expression, although the mechanisms through which the patterns of gene expression are affected remain to be determined. In a recent study of the mechanisms through which exercise impacts prostate cancer survival, it was found that 184 genes are differentially expressed between prostate cancer patients who engage in vigorous activity, and those who do not [37]. Amongst the genes that were more highly expressed in men who exercise were BRCA1 and BRCA2, both of which are involved in DNA repair processes.

Another neuropeptide which changes after exercise is Vasoactive Intestinal Protein (VIP). Breast and prostate cancer patients have been found to have higher VIP titres compared to individuals who regularly exercise, and who have increased production of natural anti-VIP antibodies[45]. In hormone-related cancers such as cancers of the breast, ovaries, prostate and testes, the association between high levels of circulating sex hormones and cancer risk is well established[46]. Another mechanism through which exercise may affect cancer, is through decreasing the serum levels of these hormones. For breast cancer survivors, the link between exercise and lower levels of oestrogen has been shown[13,34,47]. An indirect, related mechanism is that exercise helps reduce adiposity, and adiposity in turn influences the production and availability of sex

hormones[48]. In addition, greater adiposity leads to higher levels of Leptin, a neuropeptide cytokine with has cancer promoting properties[49,50].

Other pathways include the modulation of immunity, such as improvements in NK cell cytolytic activity 11; the modulation of apoptotic pathways through impacting on a key regulator, p53[51], and an exciting recent discovery, the messenger protein irisin, which is produced in muscle cells in response to exercise and is found is to be an important molecule in linking exercise to the health benefits[52], However, we are only beginning to scratch the surface with these and the other mechanisms discussed here, and much more research needs to be done to in this area.

Incorporating exercise into mainstream cancer management

The challenge for health professionals is how to encourage and motivate individuals with cancer to increase their exercise levels. Some, of course, are motivated to increase physical activity or remain active after cancer. However, a recent survey of 440 men with prostate cancer found that only 4% of patients exercised for more than the 3 hours a week recommended by the WCRF[17]. Macmillan Cancer Relief has produced a series of helpful booklets and web-based patient information materials designed to inform and motivate individuals to exercise as part of its *'Move More'*programme. The Cancernet website has a facility to search for local exercise facilities by postcode, which can be an aid for health professionals when counselling patients. It highlights activities that men will hopefully find feasible and enjoyable such as golf, exercise groups and walking groups, and are encouraged to attend in addition to work place activity and gardening.

Several pilot schemes have been started throughout the UK with the aim to incorporate exercise programmes into standard oncology practice. The difficulty with small schemes is that they tend to be poorly funded, often poorly attended and are unlikely to be sustainable in the longer term. Many agree that the gold standard model would be similar to the cardiac rehabilitation programme[53]. This would involve a hospital scheme run by a physiotherapist or an occupational therapist, supervising patients immediately after surgery, radiotherapy and even during chemotherapy. This is followed by refering the patient to a community-based scheme for the longer term. Unfortunately, this type of scheme is expensive and unlikely to be funded at present, despite the obvious savings by preventing patient relapsing and ultilising health care facilities to help late effects of cancer treatment[54]. However, expanding existing services, such as the National Exercise Referral Scheme, is a practical solution. The National Exercise Referral Scheme exists for other chronic conditions such as cardiac rehabilitation, obesity and lower back pain. The national standards for the scheme to be expanded to include cancer rehabilitation were written and accepted in 2010. Training providers have now developed training courses for exercise professionals set against these standards. Trainers completing the course gain a Register of Exercise Professionals (REPs) Level Four qualification, allowing them to receive referrals from GPs and other health professionals.

Conclusion

There are a wealth of well-conducted studies which have demonstrated an association between regular exercise and lower risk of side effects after cancer, as well as reasonable prospective data for a lower relapse rates and better overall survival. However, as there are several overlapping lifestyle factors, which are difficult to investigate on their own, there remain some concerns that exercisers may do better in these studies because they are less likely to be over-weight, more likely to have better diets and to be non-smokers. Although the existing RCTs provide encouraging evidence that exercise intervention programmes are beneficial, further large RCTs are needed, particularly in terms of cost-effectiveness, before commissioner's start investing more in this area.

Competing Interests
None declared
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