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 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 tumor 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.

Key words: 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 [ACS 2012]. 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 2022. 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 alive for longer with metastatic disease. 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 recognized by health professionals, advocacy groups and charities; it still remains an under utilized 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 that plague individuals in the cancer survivorship period. The adverse effects shown to be alleviated by exercise include cancer-related fatigue, muscle weakness, thromboembolism, weight gain, loss of bone density, quality of life, psychological distress, incontinence, and sexual dysfunction [Fong 2011, Thomas 2009 Thomas 2009, Thomas et al 2012]. In addition, we review the emerging evidence that exercise may slow the progression of some cancers [Ornish 2005, Thomas 2009, Thomas 2007, Thomas 2007] reduce the risk of overall death from cancer [Chlebowski 2002, Kenfield 2011, Haydon 2006], as well as reducing the probability of relapse [Schmitz 2010, Markes 2006, McNeeley 2006], and discuss the possible biochemical basis for these effects.

Physical activity improves well-being after cancer

Dozens of interventional studies have tested the feasibility and potential benefits of exercise in cancer survivours [Schmitz 2010, Markes 2006, McNeeley 2006]. Recent meta-analysis of randomized 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 showed a benefit for a number of troublesome symptoms particularly, fatigue; mood, anxiety and depression; muscle

power, hand grip and exercise capacity and quality of life [Fong 2012].

The American College of Sports Medicine also published a comprehensive review of exercise intervention studies in cancer populations that included data from 85 RCT's of exercise in cancer survivours. Evidence consistently demonstrated that exercise could safely be performed 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 [Schmitz 2010]. The individual categories of symptoms which commonly afflict cancer survivours 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 hormone or biological therapies [Wagner 2004]. The first step to treating CRF is to correct, if possible, any medical conditions that may aggravate it, such as anemia, electrolyte imbalance, liver failure and nocturia; or to eliminate drugs such as opiates, anti-histamines and anti-sickness medication [Thomas 2005]. Exercise programmes have also been shown to improve this symptom in three meta-analyses. The first reviewed 28 randomized controlled trials (RCTs) involving 2083 participants in a variety of exercise programmes and showed that exercise improved CRF, although the benefit overall was small [Cramp 2008]. The second reviewed 18 RCTs involving 1109 participants, and sub-divided the data into home-based exercise programmes and supervised exercise programmes, which included a combination of aerobic and resistance exercises [Velthuis 2010]. In this study, a statistically significant benefit of exercise for CRF was observed in breast cancer patients involved in supervised exercise programmes but not home-based programmes [Velthuis 2010]. The meta-analyses mentioned above found a small to moderate reduction in CRF among breast cancer survivors assigned to exercise programmes [Fong 2012, Schmitz 2010]. Overall, more studies involving supervised aerobic exercise programmes have reached statistical significance and the degree of improvement has been better for patients in supervised exercise programmes than in the home-based programmes [Cramp 2010, Ballard-Barbash 2012].

Psychological distress, including anxiety and depression, is common after cancer with reported prevalence rates of 25-30% [Drouin 2005]. Patients with psychological distress have also been shown to have reduced survival compared to those who are psychologically healthy [Kadan-Lottick 2005]. 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 [Mock 2010]. The recent meta-analysies of RCTs also demonstrated a reduction in anxiety and depression among individuals assigned to exercise programmemes [Fong 20012, Schmitz 2010].

Quality of life (QOL) is also known to be lower in cancer sufferers and survivors, possibly as it is in many ways linked to other physical and psychological symptoms of cancer and its treatment. Meta-analysies 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 [Fong 20012, Schmitz 2010]. For example, in a study involving 1966 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 [Lynch 2008]. 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 [Courneya 2007].

Weight gain is of concern for many cancer patients, as 45% of women with breast cancer report significant weight gain [Meyerhardt 2006], and in a study of 440 prostate cancer survivors, 53% were overweight or obese [Thomas 2001]. 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) [Meyerhardt 2006]. The reasons for this are multifactorial but may include other symptoms of cancer treatment such as fatigue and nausea causing the 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 [Knols 2005]. 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 [Chlebowski , Segal 2009, Knols 2005].

Bone mineral density (BMD) depletion is a considerable concern among both male and female cancer survivors. Pre-menopausal women who have had breast cancer treatment are at increased risk for osteoporosis due to reduced levels of estrogen 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 for 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 [Brown 2003, Saad 2008]. Lifestyle factors linked to an increase 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 [Ryan et al 2007 Weikert et al 2005, Marini et al 2008]. Fortunately, a number of studies have linked regular physical activity with a reduction in the risk of bone mineral loss. In one controlled trial, 66 women with breast cancer were randomized to a control group or an exercise programme of either resistance exercise (using bands) or aerobic exercise (fast walking or jogging) [Waltman 2010].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 [Waltman 2010]. In another RCT of 223 women with breast cancer, it was found that exercise helps preserve bone mineral density even when bisphosphonates (risedronate), calcium (1500mg /day) and vitamin D (400 IU /day) had already been prescribed [Schwartz 2007]. In this study, women who exercised for over 30 minutes 4-7 times a week had significant improvements in BMD compared to the medication-only group [Mackey 2005].

Thromboembolism remains a significant risk for patients with malignancy, particularly those with pelvic involvement, recent surgery, immobility, a previous

history of varicose veins or thrombosis or receiving chemotherapy [Galster 2005]. 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 [Knols 2005, Davis 2011].

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 [Davis 2011].

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 improves overall survival and reduces the probability of relapse. One of the most convincing studies to provide evidence of a survival benefit comes from an RCT where 2,437 post-menopausal women with early breast cancer were randomized to nutritional and exercise counseling, or no counseling, as part of routine follow-ups [Chlebowski 2002]**.** In the group receiving counseling, less women relapsed and overall survival was greater. Another RCT involved men with early prostate cancer were randomized to an exercise and lifestyle intervention or standard active surveillance found that the average PSA in the intervention group went down, while in the control group it went up [Ornish 2005]. This supports a previous RCT which primary end point evaluated a salicylate based food supplement but in required men in both arms received exercise and lifestyle counseling. Although the was no difference in the primary end point 34% men, who's PSA was climbing before trial entry, stablised [Thomas 2007].

The most comprehensive ongoing study looking at physical activity and outcome is the CHALLENGE study (colon Health and Lifelong Exercise Change). It is randomising 962 individuals with stage 2 or 3 colon cancer into an intensive supervised exercise programme or stand care. End point will include DFS, Qol, Health related fitness and biomarkers.

The majority of the other published evidence for a reduced relapse rate and improved survival after cancer originate 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 then prostate [Ballard-Barbash 2012]. The most notable are summaries below:

Breast cancer; The six most prominent prospective cohort studies, included, in aggregate, more than 15,000 women have examined the relationship between physical activity cancer and prognosis. The general trend was that women who exercise between >2.5-3 hours / week had a between a 35-67% lower risk of relapse and a 35-49% lower risk of cancer-specific death:

- Irwin et al. (2008) investigated a cohort of 933 breast cancer survivors and found that those who consistently exercised for >2.5 hours per week after diagnosis had approximately a 67% lower risk of all deaths compared to women who were not physically active.
- Holmes et al. (2005) performed a separate evaluation of 2987 women in the Nurses' Health Study and found that women with breast cancer who were walking >3 hours a week had lower recurrence rates, and better overall survival.
- Holick et al (2008) performed a prospective observational study of 4482 breast cancer survivors and found that women who were physically active for >2.8 hours per week had a significantly lower risk of dying from breast cancer (35-49% reduction).
- Pierce et al (2007) found that the benefits of 3 hours of exercise were even greater if combined with a healthy diet.
- Sternfeld et al (2009) The LACE study evaluated 1870 women with breast cancer within 39 months of diagnosis. There was a significant difference in overall death rate between the highest and lowest quartile of exercise levels.
- Chen et al (2001). The Shanghai Cancer Registry Study evaluated 4826 women with breast cancer at an average of 36 months after diagnosis. Women who exercised .8.3 METS/week compared to sedentary women had a lower breast and cancer death rate and better overall survival

Colorectal: The scientific community are eagerly waiting the results of the CHALLENGE RCT mentioned above but a number of retrospective analysies of randomised chemotherapy and cohort trials demonstrate a correlation between those physically active and reduced relapse rates of between 14-50%:

- Haydon et al. (2006) retrospectively analysised a RCT involving patients with stage III bowel cancer and found had a significant association between exercise and a 31% reduction in relapse rate.
- Giles et al (2002) evaluated physical activity levels amoung 526 patients who had been recruited into the Australian cohort study between 1990-4. They found that those participating in recreational sport 1-2 days week during which they became sweaty and breathless had a 5 year overall survival of 71% opposed to 57% in non exercisers. The significant absolute difference of 14% was statistically strongest in men with stage III disease.
- Meyerhardt et al (2006) found in a similar analysis of the Intergroup CALGB 89803 study. Patients with bowel cancer found a 35% reduction in relapse rate in physically active patients after chemotherapy**.**

- Meyerhardt et al (2009) also analyised 668 patients with colorectal cancer within the Health professionals Study who were between 6months to 4 years post diagnosis. Men who exercised >27 v < 3METS-h / week had a lower cancer specific mortality.

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Prostate: Tree cohort studies have demonstrated a survival benefit for physically active men with prostate cancer, although the evidence overall is not as comprehensive as for breast and colorectal cancer survivors:

- Kenfield et al (2012) performed a subset analysis of 2,686 men with prostate, within the Health Professional Study, who exercised >30minutes per week or $\geq$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 or more had a 51% lower risk of overall death.

- Richman et al (2011) 1455 men with prostate cancer walking more than 3 hours a week correlated with an improved survival but only if >3miles/hour.
- Giavannucci EL, (2005) 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.

Evidence is lacking for other cancer types but many would argue that if similar benefits are seen across the more common cancer types, this benefit is very likely to be applicable to patients with other cancers. Further well conducted trials are clearly need and are planned in many academic centres across the World including the large RCT involving over 200 men with prostate cancer, which is near completion and involves exercise advice as well as a polyphenol-rich supplement known as Pomi-T (Pomi-T study).

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 [Kenfield 2011]. 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 [Richmond 2011]. 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.

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 that 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 term and the long term, and they can judge the optimal exercise levels to improve fatigue and not aggravate it.

The underlying mechanisms of the anti-cancer effects of exercise

The biochemical mechanisms through which exercise has a positive impact on the side effect profile and survival of cancer patients remains incompletely understood. However, the chemical environment of blood appears to be better after exercise, as shown in a recent RCT [Ornish 2005]. In this study, it was 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 [Ornish 2005]. The precise factors responsible for the anti-cancer mechanisms are not well defined, but may include changes in the levels of growth factors such as insulin-like growth factors (IGFs), estradiol and other hormones, as well as specific effects on gene expression patterns and immunity.

One of the best understood mechanisms through which exercise may prevent cancer or improve survival are 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. After binding to its receptor tyrosine kinase, IGF-1 activates several signaling pathways including the AKT pathway, leading to the inhibition of apoptosis and the promotion of cell growth and angiogenesis [Yu 2000, Frierer 1999]. Higher levels of IGF-1 would therefore be expected to increase tumor growth, and has been reported to be associated with cancer risk [Palmqvist 2002]. An inverse relationship of cancer risk with IGFBP3 levels has also been shown, although this effect has not been confirmed in all studies [Ma 1999]. 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 [Haydon 2006]. Decreased levels for IGF-1 in physically active patients have also been reported with an associated survival benefit [Irwin 2009]. One mechanism through which exercise

may improve survival from cancer is therefore through the modulation of the availability of growth factors (see table 2).

Exercise has also been shown to have large impacts on gene expression, though 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 [Kenfield 2011]. Among the genes that were more highly expressed in men who exercise were BRCA1 and BRCA2, both of which are involved in DNA repair processes. Though more research needs to be done to clarify the mechanisms, one way in which exercise may lead to greater survival is through impacting on DNA repair.

Another neuropeptide which changes after exercise is Vasoactive Intestinal Protein (VIP) [Power . Breast and prostate patients have been found to have higher VIP titres compared to individuals who regularly exercise who have increased production of natural anti-VIP antibodies [Velijkovic 2012]. 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 [Kaaks 2002]. One mechanism through which exercise may affect cancer risk and survival is through decreasing the serum levels of these hormones. For breast cancer survivors, the link between exercise and lower levels of estrogen has been shown [Haydon 2006, Irwin 2009, Folkert 2010]. An indirect related mechanism is that exercise helps reduce adiposity, and adiposity in turn influences the production and availability of sex hormones [Friedenreich 2010]. In addition, greater adiposity leads to higher levels of Leptin, a neuropeptide cytokine with has cancer promoting properties [Hoffmann-Goetz 1998]. Exercise may therefore indirectly also influence the levels of Leptin through its effects on body weight and composition [Surmacz 2007].

Other pathways through which exercise may impact on survival from cancer include the modulation of immunity, such as improvements in NK cell cytolytic activity [Fairey 2001] and the modulation of apoptotic pathways through impacting on a key

regulator, p53 [Sharafi 2012]. 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, particularly to establish the links between exercise and the factors that are up-regulated or down-regulated in response to it. An exciting recent discovery is 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 [Boström 2012], though more work needs to be done to establish the pathways affected by this molecule.

Incorporating exercise into mainstream cancer management

The challenge for health professions 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 the patients exercised more than the 3 hours a week recommended by the WCRF [Thomas 2013]. 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 professional when counselling patients. It highlights activities that men will hopefully find feasible and enjoyable such as golf, exercise groups and walking groups, which men 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 [Jolliffee 2003]. This would involve a hospital scheme run by a physiotherapist or an occupational therapist supervising patients immediately after surgery, radiotherapy and even during

chemotherapy, and then refering the patient to a community based scheme for the long 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 [Thomas 2009]. 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, and the national standards for the scheme to be expanded to include cancer rehabilitation were written and accepted in 2010. Charities such as The Wright Foundation have now developed training courses for exercise professionals set against these standards [Wrightfoundation]. The course empower trainers to be more confident in helping cancer survivors to exercise by providing an insight into cancer treatment, how treatments affect the ability to exercise as well as teaching trainers to deal with altered body image, peripheral neuropathy, hand foot syndrome, fatigue and other cancer-related side effects. Trainers completing the course gain a Register of Exercise Professionals (REPs) level four qualificaton 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 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 in better health before cancer treatments, are less likely to be over-weight, and 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.

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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

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	Estrogen	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