



Cancer: the role of exercise in prevention and progression

Cancer: the role
of exercise

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Abstract

Purpose – The paper's purpose is to examine evidence for the benefits of exercise in relation to cancer development, progression and prevention.

Design/methodology/approach – The reviewed literature was divided into categories according to the role exercise plays in cancer prevention and progression, during treatment, and in relapse prevention.

Findings – There is now persuasive evidence that exercise improves the physical and psychological function of patients with cancer, reduces the risk of recurrence and possibly improves survival.

Originality/value – Previous research highlights the importance of exercise in cancer prevention and throughout the cancer experience. However, current knowledge of the mechanisms by which physical activity may positively influence the activity of cancers is poorly understood; these mechanisms are explored in this paper.

Keywords Cancer, Exercise, Personal health

Paper type Literature review

Introduction

Regular exercise has long been known to improve psychological and physical well-being and reduce the risk of life threatening illnesses including stroke, cardiovascular disease and cancer (Knols *et al.*, 2005). There is now compelling emerging evidence that exercise also has fundamental benefits after a diagnosis of cancer in terms of well-being, reducing cancer progression and preventing its relapse. The caveat for reviewing the published data on exercise trials is that people who exercise regularly often follow other health-seeking behaviour. It is therefore difficult to separate the evidence for exercise from other confounding risks such as diet, smoking, body size, supplements and analgesic intake (Chan *et al.*, 2005; Chlebowski *et al.*, 2005; Sonn *et al.*, 2005). Nevertheless, this article reviews the available published evidence for the benefits of exercise in relation to the categories of cancer prevention, reduction in progression, reduction in the risks of therapy and preventing relapse.

Method

The reviewed literature was divided into categories according to the role exercise plays in cancer prevention and progression, during treatment, and in relapse prevention.

Results

Exercise and cancer prevention

There are now multiple studies which demonstrate an association between obesity, exercise, and colorectal cancer incidence and mortality (Haydon *et al.*, 2006; Quadriatero and Hoffman-Goetz, 2003). It has been estimated that being overweight or obese could account for 14 per cent of male and 20 per cent of female cancer deaths in the UK (Hall, 2005). The incidence of many cancers increases in Asian men following



migration to North America and Europe compared to their native counterparts (Shimizu *et al.*, 1991). This implies that environmental factors contribute to the risk in addition to genetics alone. Several epidemiological studies have shown that these factors relate to a stereotypical western lifestyle which includes; high fat and red meat consumption, low intake of fresh vegetables and fruit and low levels of exercise (Chan *et al.*, 2005; Sonn *et al.*, 2005; Wilkinson and Chodak, 2003). For colorectal cancer, for example, most cohort studies have demonstrated a reduction in the order of 40-50 per cent for those at the highest levels of physical activity, with many demonstrating a dose-response relationship (Friedenreich and Orenstein, 2002). This percentage indicates that increasing physical activity may be the most important risk factor that is amenable to modification by individuals wishing to reduce their risk of this common malignancy.

Exercise and cancer progression

The most reliable data in this category comes from patients with indolent or relapsing prostate where the slow progression allows time for alternative interventions (Thomas, and Woodward, 2006). Data are emerging from epidemiological and prospective studies that environmental factors mediate the transformation of latent prostate cancer into clinically apparent cancers and dietary and lifestyle changes may influence this process (Chan *et al.*, 2005; Sonn *et al.*, 2005; Wilkinson and Chodak, 2003). Randomised data on a reduction of cancer progression in men with established prostate cancer are currently scant, but a recent study has generated enormous media attention and interest from patient advocacy groups (Ornish *et al.*, 2005.) In this study, 93 volunteers with early prostate cancer from the USA, who had opted not to undergo conventional therapies, were randomly assigned to intensive nutritional counselling and lifestyle changes, or not, as part of their active surveillance. The lifestyle changes in this study included a vegan diet supplemented with soy, vitamin E, fish oils, selenium and vitamin C, together with a moderate exercise program (30 min walking six days a week) and stress management techniques such as yoga. The prostate-specific antigen (PSA) decreased at 12 months in the intervention group (by 4 per cent) but increased in the control group (by 6 per cent) and this was statistically significant ($p = 0.016$). As a secondary end point, serum taken from patients from the intervention group and introduced to prostate cell lines *in vitro* were eight times more likely to inhibit their growth than the control arm (70 per cent vs 6 per cent, $p < 0.001$). Furthermore, changes in PSA and cell line growth strongly correlated with the degree of lifestyle changes. These data are encouraging and promising but need to be substantiated in larger multicentre studies. In the UK, a small pilot study investigating lifestyle intervention combined with a salicylate compound (Thomas *et al.*, 2005) demonstrated PSA stabilisation in a subgroup with prostate cancer. A double blind randomised, multicentre, controlled trial is underway under the registration of the NCRN.

Exercise during cancer treatments

Although cancer-related fatigue, nausea and pain are considerable disincentives for patients to exercise during cancer therapies, there is now compelling evidence for a benefit across a wide range of ailments.

Fatigue, reported to be the commonest side-effect in 65-90 per cent of patients receiving chemotherapy and 80-90 per cent of those receiving radiotherapy, has been demonstrated to influence patients nutritional state, increase morbidity and negatively affect chemotherapy dose intensity (Iop *et al.*, 2004). Regular light exercise has been

shown to improve fatigue and quality of life issues for patients with cancer, particularly those on chemotherapy (Dimeo *et al.*, 1999; Schwartz *et al.*, 2001).

Thromboembolism remains a significant risk for patients with malignancy, particularly those with pelvis, recent surgery or immobility, or a previous history or receiving chemotherapy. Although strategies such as compression stockings, warfarin and low molecular weight heparin are essential, exercise remains a practical additional aid in reducing this life threatening complication (Knols *et al.*, 2005).

Body composition, particularly, weight gain during and after adjuvant chemotherapy, is becoming an ever-increasing significant concern. Women with breast cancer, for example, report a 45 per cent incidence of significant weight gain often at a time in their lives that makes losing it difficult. The reasons are multifactorial. Some patients concerned about weight loss, perhaps from dated and misleading information sources, tend to over eat. Others, with fatigue and nausea, stop exercising. Drugs including steroids and hormone therapies such as tamoxifen are also exacerbatory factors. Whatever the cause, numerous prospective exercise intervention studies have demonstrated significant improvement in body fat and lean mass indices (Knols *et al.*, 2005; Winningham *et al.*, 1989). Likewise, benefits for exercise have been demonstrated for bone mineral density, muscle strength and walking distance, all potential risk factors post chemotherapy (MacVicar *et al.*, 1989).

Psychological well-being, such as mood status, depression, anxiety and panic disorders are commonly under diagnosed in up to 50 per cent of patients with cancer (Knols *et al.*, 2005). Cohort studies have suggested that depressed patients, for example, with lung and breast cancer have a reduced survival than those who are psychologically healthy (Kadan-Lottick *et al.*, 2005). A number of prospective exercise intervention studies among patients receiving therapies ranging from chemotherapy, radiotherapy and hormone therapies have demonstrated reduced levels of depression, anxiety and improved mood and quality of life (Mock *et al.*, 1997, 2001; MacVicar *et al.*, 1989).

Constipation caused by immobility, opiate analgesics or antiemetics during chemotherapy remain a significant patient concern. Exercise reduces bowel transit time and ameliorate constipation and its associated abdominal cramps (Knols *et al.*, 2005).

Exercise to prevent relapse

A prospective, randomised trial involving 2,437 women with early breast cancer involved randomisation to receive nutritional and lifestyle counselling, or not, as part of routine follow-ups. There was a statistically significant improved disease-free survival in the intervention arm, particularly, in women oestrogen receptor negative (Chlebowski *et al.*, 2005). A cohort study of 526 cases of colorectal carcinoma that demonstrated a 31 per cent reduction in cancer deaths for the physically active compared with the physically inactive across all stages (Haydon *et al.*, 2006). The benefit was greatest for stages II and III disease, with a hazard ratio for colorectal cancer (CRC)-specific survival of 0.49 (adjusting for age, sex and stage) in this subgroup. Another study that reported outcomes for 816 stage III colon cancer patients receiving adjuvant chemotherapy found a 35 per cent improvement in disease-free survival for individuals in the highest quintile of regular physical activity compared with the lowest quintile (Meyerhardt *et al.*, 2005).

Exercise has further been found to influence the psychological status of women who remain active after breast cancer treatment. Statistically significant results have been reported for self-report outcomes of mood status, fatigue, depression, anxiety,

happiness, self-esteem and quality of all (Courneya *et al.*, 2003; McKenzie and Kalda, 2003; Pinto *et al.*, 2003), all of which can largely influence overall health and well-being. It is difficult to know how good exercise is for an individual but some organisations have tried to quantify it. The Harvard Centre for Cancer Control, for example, estimates that at least 15 per cent of colon cancers could be prevented by 30 minutes daily exercise (Hall, 2005).

Mechanisms of benefit

A number of studies highlight the importance of exercise in cancer prevention and throughout the cancer experience. However, our current knowledge of the mechanism by which physical activity may positively influence the behaviour of cancers is poorly understood. One mechanism relates to body fat constitution: a report by the US Surgeons General estimated that obese men were 33 per cent more likely to die of cancer than those of a normal weight and obese women had a staggering 55 per cent increased risk of dying from cancer (Haydon *et al.*, 2006; Hall, 2005). Associations of adiposity and outcome after cancer treatments have been observed for CRC (Haydon *et al.*, 2006; Meyerhardt *et al.*, 2005) but also for breast (Holmes *et al.*, 2005; Malin *et al.*, 2005) and prostate (Giovannucci *et al.*, 2005) cancer, with the improvement in survival being a result of decreased cancer deaths rather than reduced death (Amling *et al.*, 2004; Chlebowski *et al.*, 2002). Although seemingly obvious, the observation that exercise helps to reduce weight among patients with cancer is supported by a prospective study which reported a significant decrease in body fat after physical exercise intervention (Burnham and Wilcox, 2002). The mechanism of risk of being overweight for breast and endometrial cancer may lie in their higher oestradiol levels which has been reported to lower following weight reduction programmes (Wu *et al.*, 1999). For colon cancer, exercise may work by reducing the bowel transit time, reducing the time that potentially carcinogenic substances are in contact with the bowel wall. Exercise also helps control the body's levels of serum lipids and cholesterol, high levels have been particularly associated with greater risk of advanced disease (Harvei *et al.*, 1997; Kristal *et al.*, 2002), particularly in men with prostate cancer where lower serum lipids correlated with lower testosterone (Barnard *et al.*, 2003; Chan *et al.*, 2002; Pollak *et al.*, 2004).

Other theories include alterations in prostaglandin levels/ratios, and through effects on the immune system (Quadrilatero and Hoffman-Goetz, 2003; Meyerhardt *et al.*, 2004; Westerlind, 2003). The most compelling emerging evidence supports the idea that physical activity might exert its beneficial effect via the insulin-like growth factor (IGF) axis (Giovannucci, 2001; Kaaks *et al.*, 2000; McTiernan *et al.*, 1998). A number of cohort studies have shown an increased risk of cancer, particularly colorectal, with higher levels of insulin-like growth factor 1 (IGF-1) and C peptide, and an inverse relationship with insulin-like growth factor binding protein 3 (IGFBP-3) levels (Giovannucci *et al.*, 2000; Ma *et al.*, 1999, 2004; Nomura *et al.*, 2003), although this effect has not been confirmed in all studies (Palmqvist *et al.*, 2002; Probst-Hensch *et al.*, 2001). The benefits of lowering IGF-1 may be linked to its central role in the growth regulation processes. The main stimulus for IGF-1 production comes from growth hormone (Kaaks and Lukanova, 2002). This stimulatory effect of growth hormone is modulated by insulin, which increases growth hormone receptor levels and in turn IGF-1 (Firth and Baxter, 2002; Suikkari *et al.*, 1988). Early studies have shown that after binding to its receptors, which are found on normal colonic mucosal cells as well as colon cancer cells, IGF-1 can stimulate cell proliferation, inhibit apoptosis (Yu and Rohan, 2000) and promote

angiogenesis (Freier *et al.*, 1999; Warren *et al.*, 1996). In the circulation, as over 90 per cent of IGF-1 is bound to IGFBP-3, binding inhibits the action of IGF-1 by limiting the availability of free hormone although IGFBP-3 is also known to have actions independent of IGF-1, including the ability to induce apoptosis (possibly via the tumour suppressor gene p-53) (Hong *et al.*, 2002; Valentinis *et al.*, 1995; Williams *et al.*, 2000), and inhibit growth via the transforming growth factor pathway (Rajah *et al.*, 1997). The most convincing evidence comes from a cohort study of 41,528 people aged between 27 and 75 years with colorectal cancer recruited between 1990 and 1994 in which they had previously demonstrated a prognostic benefit of physical activity. This and another large prospective cohort study from Melbourne Australia both reported statistically lower levels of IGF-1 and higher IGFBP-3 in those physically active prior to diagnosis and these collated with disease specific survival and overall survival (Giles and English, 2002).

Discussion

As illustrated in the reviewed literature, a number of methodological limitations confound the interpretation of the benefits of exercise from other risks such as diet, smoking, body size, supplements and analgesic intake. Nevertheless, despite these caveats there is now persuasive evidence that exercise improves the physical and psychological function of patients with cancer, reduces the risk of recurrence and possibly improves survival. Above all, life-enhancing behaviour after a diagnosis of cancer can increase the degree of self-empowerment for both the patients and carers who can also join in with the activity. Patients who feel empowered in their own management process have long been known, from both randomised (McHugh *et al.*, 1995; Thomas *et al.*, 2000) and prospective observational studies (Deustch *et al.*, 1992), to be more satisfied and to have better psychological adjustment to their illness. Furthermore, no trial has shown that exercise following a diagnosis of cancer is harmful.

As a consequence there is enough evidence to formally encourage patients to exercise, where reasonable, as part of routine oncology practice. Although individual patient motivation is the strongest determinant of the intensity of exercise the physician plays a fundamental role in promoting exercise to aid well-being, as demonstrated by one study finding that patients who were encouraged by their oncologist exercised significantly more than patients who did not receive such encouragement (Segar *et al.*, 1998). This encouragement is especially important with patients who may be avoiding exercise due to fatigue and other side-effects of treatment.

Another basic strategy is to include a general exercise advice sheet for patients embarking on cancer therapies, a policy adopted by our and a number of UK Oncology Units (Table I). Following cancer therapies, more comprehensive information strategies may be required, as some patients who may even have exercised well before their diagnosis may not have the same motivation or abilities afterwards. The cancer itself, surgery or the anticancer therapies, have caused physical disability, notwithstanding the commonly associated general, fatigue, weight gain and reduced esteem in their body image. Patients may have to relearn their exercise patterns and consider a broad range of activities, particularly, which they may not have previously contemplated. Another strategy currently being tested within our centre is the measurement of health baselines (Davies and Kinman, 2006) via the health baseline comparison questionnaire and how these baselines change throughout the treatment process. This could be

Lifestyle category	Advice courtesy of www.cancernet.co.uk/exercise
Generally	Exercise should not just be a passing fad but be incorporated into our daily lives for the rest of our lives. During the day we have several choices, which require more or less levels of exertion. Try to take the more active option Walking instead of using the car for short journeys. Try getting off the bus or tube one stop earlier
Home	If you like exercising at home it is worth having a semi-formal programme to follow. There are many useful gadgets available to make it more fun (exercise bikes, treadmills, rowing machines, etc). Alternatively, follow an exercise video – there are many good ones available. When watching TV try to get up and walk around for a few minutes at every break
Office	Use the stairs instead of the lift. If possible take a walk for some exercise at lunchtime. Try desk exercises – you may look odd but they can keep you alert especially when you get tired or sleepy. Do not worry about the comments – people will secretly admire your enthusiasm
Social life	There is an alternative to the pub or the TV. Exercise can and should be sociable and enjoyable – find something which is fun otherwise you will give it up very quickly
Walking	In addition to integrating walking in our daily duties, social walking groups are available in many areas and are a good way to meet new people, view interesting scenery and exercise to a variety of ability levels. Golf is a good encouragement to walk and clubs are available throughout Britain for all levels
Cycling	Cycling socially with family or part of a daily commute even if only once or twice a week can be fun and even save money. Consider buying a bike with a basket for the shopping
Gym	Joining a gym is always a good start. Paying money every month is a good incentive to use it. Even if you are overweight or unfit do not worry as so are most other people and nobody of worth will criticise your efforts
Exercise classes	There are numerous enjoyable ways to exercise in groups at a variety of levels. Your local sports centre will also have many activities from five-a-side football, squash, badminton, volleyball, netball as well as numerous exercise aerobics classes
Swimming	Many pools offer classes to learn to swim, single sex or disabled
Dance	There are numerous dance classes available in most towns from traditional ballroom, line dancing, ballroom to Rock and Roll or Salsa

Table I.
Patient tips to increase
exercise activities

implemented further by measuring baseline exercise levels in an attempt to help patients make appropriate adjustments to exercise and lifestyle. This could further aid patients in the development of adapted exercise baselines that can be maintained and that can subsequently enhance well-being and quality of life. Maybe the future would be rehabilitation exercise classes as part of a routine Oncology Unit. In the mean time patients could be directed towards the myriad of council or independent exercise activities available locally. Cancernet.co.uk is able to search for a comprehensive range of activities by post code, ranging from ballroom, line and salsa dance lessons, aerobics, yoga and fitness classes, local walking, swimming and cycling groups through to gyms, sport centres, tennis and badminton courts, palates and personal trainers, giving times, contact numbers and locations. Even if patients do not have access to the internet, information on these local activities could be printed out as necessary during patients' treatment pathway.

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