Exercise and cancer survivorship

The association between exercise and cancer incidence has long been established. Increasingly research is considering the role of exercise in the oncology setting. This article summarizes the current evidence for exercise promotion in cancer survivors and guidelines for exercise participation in this population.

Advances in cancer detection and treatment have meant that survival rates for many types of cancer have increased steadily over the past 40 years, with 10-year survival rates for all cancers increasing from 24% to 45% between 1971 and 2007 (Cancer Research UK, 2009). The trends towards an ageing population (and therefore more cancer diagnoses), coupled with continuing advances in early detection and treatment, means the estimated 2 million 'cancer survivors'* in the UK today is expected to increase by 3% year on year (Maddams et al, 2008).

Improvements in survival are immensely encouraging for those facing a cancer diagnosis, but survival can be accompanied by physical and psychosocial difficulties. Treatment side effects include nausea, pain, weight gain and insomnia, and cancer-related fatigue is reported by up to 96% of cancer survivors (National Cancer Institute, 2010). In addition, some survivors experience impairments in physical function, anxiety, depression and reductions in quality of life. While these cancer-related sequelae are most apparent during the treatment period, they can persist for months and even years after treatment. Additionally, in the years following successful cancer treatments, survivors are at an increased risk of developing other comorbidities including cardiovascular disease, diabetes, osteoporosis and second primary cancers (Wingo et al, 1998; Demark-Wahnefried et al, 2005; Travis, 2006). Consequently the growing population of cancer survivors and the associated long-term and late effects of cancer treatment and chronic disease burden has been recognized as a public health priority in the UK (Department of Health, 2007).

Epidemiological studies have consistently shown an inverse association between physical activity and the incidence of numerous cancers (e.g. World Cancer Research Fund/American Institute for Cancer Research, 2007), but investigating the role of exercise in the oncology setting is a relatively recent phenomenon. What is now becoming clear is that exercise may offer a safe and effective means of ameliorating many cancer-related sequelae, both during and after treatment, as well as relieving some of the additional disease burden faced by cancer survivors.

Dr Chloe Grimmett *is Research Associate in the Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, London WC1E 6BT*

This article will comment on current evidence for the role of exercise in the oncology setting during and after treatment, its effect on treatment-related symptoms, as well as the potential role in improving longer term cancer prognosis. Information on the current guidance for the prescription of exercise among this population will also be discussed.

Exercise during and after cancer treatment

Historically, medical professionals have encouraged cancer patients to rest in an attempt to manage symptoms related to cancer treatment such as fatigue and reduced physical function. However, it has now become apparent that reducing daily activities may exacerbate the problem, resulting in an accelerated decline in physical function, deterioration in cardiorespiratory fitness and loss of bone density, and in some cases a vicious cycle of further reductions in activity.

In the last decade there has been a surge in studies designed to determine whether exercise has a role to play in improving the health and wellbeing of cancer survivors, and numerous reviews have been published examining the effect of exercise on treatment-related symptoms and other physiological and psychosocial factors. Some have focused on one specific outcome such as cancer-related fatigue (Cramp and Daniel, 2008) or quality of life (Courneya and Friedenreich, 1999), while others have taken a more extensive look at a range of symptoms and health outcomes (Galvao and Newton, 2005; Knols et al, 2005; Schmitz et al, 2005; Conn et al, 2006).

These reviews have varied in their inclusion criteria and the time point of interest (i.e. during or after treatment). Some of the early reviews were qualitative in nature, including all published trials regardless of methodology, and often combining trials conducted during and after cancer treatment. Given that this field of research was in its infancy at the time these reviews were published, this was a very reasonable approach. However, more recently the number of trials has increased rapidly and, as a result, many of the latest reviews have limited their analysis to controlled trials, have included a meta-analysis, and have separated results by intervention timing.

* Throughout this article the National Coalition for Cancer Survivorship's (1986) definition of a cancer survivor will be used: 'a person is defined as a cancer survivor from the time of diagnosis and for the balance of life'.

The most recently published comprehensive review by Speck and colleagues (2010) was a systematic review and meta-analysis evaluating the effect of exercise interventions in cancer survivors during and after treatment. It provided a useful summary of the intervention characteristics. Sample sizes were generally modest, averaging approximately 40 per group, although there were some larger studies. The content of the interventions was similar to those seen in other clinical populations, with the vast majority offering aerobic exercise either alone or in combination with resistance exercise (80%). Most involved exercising 3–5 times a week at a moderate or vigorous intensity for 30–45 minutes, and the intervention period tended to be longer than 5 weeks, with 40% running for over 3 months. The authors noted a bias towards breast cancer samples, with 80% of trials conducted in this population. Conclusions were similar to those drawn from previous reviews, indicating that exercise was well tolerated both during and after the treatment period. In addition, although health practitioners often express concern over the safety of exercise among cancer patients few adverse events were reported.

Speck et al's (2010) review presented results for over 60 outcomes, including aerobic fitness, depression, immune responses and pain. The key findings during the treatment period were that patients in the exercise group experienced small-to-moderate improvements in physical fitness, upper body strength and anxiety, and moderate-to-large reductions in pain. In addition there was a consistently positive effect of exercise on immune responses such as natural killer cell activity and levels of cytokines, as well as a reduction in treatment-related symptoms such as nausea. In the post-treatment period, exercise was associated with large improvements in upper and lower body strength and a moderate effect on fatigue. Speck et al (2010) also presented data on the various facets of quality of life, whereas previous reviews had reported only on generic measures. Exercise was found to have a moderate effect on breast cancer-specific concerns after treatment completion (as measured by breast cancer-specific quality of life instruments). During the cancer treatment period, exercise had a moderate effect on physical function quality of life.

These results, in addition to those from earlier reviews, provide evidence of a consistent and positive effect of exercise during and after treatment. However, a number of important issues remain to be addressed. Because of the variety of exercise interventions delivered, it has not been possible to determine the most effective intensity, duration or mode of exercise to elicit these positive effects, nor is it known whether this varies by patient characteristics (e.g. treatment status, cancer site, stage of disease). More research is also required in patient groups other than breast cancer survivors. Inevitably there are also a number of limitations to current research. For example, there is likely a 'healthy response bias' as patients who are most unwell are less likely to agree to take part in exercise interventions. In addition not all trials provide intention-to-treat analysis, potentially inflating results. However, in the aforementioned review, loss to follow up was low (approximately 11%) which minimizes this potential bias.

One example of an attempt to overcome a number of these limitations is the work of Lee Jones and colleagues at Duke University in North Carolina. This group has carried out some excellent work among lung cancer patients, one of the more understudied groups to date. They have published a number of 'proof of principle' studies which have shown exercise interventions to be safe and feasible both in patients awaiting lung resection and those who have completed treatments (Jones et al, 2007, 2008). Peak oxygen uptake (an indicator of cardiorespiratory fitness) has been identified as a key predictor of both survival and post-surgical complications in non-small cell lung cancer patients (Pujol et al, 2009; Jones et al, 2010a), indicating that lung cancer patients have much to gain from improving cardiorespiratory fitness. A randomized controlled trial is currently underway to determine the most effective means of increasing peak oxygen uptake in this population (Jones et al, 2010b). The results of this study will provide evidence for the most effective type of exercise in a specific patient group at a defined point in the cancer pathway. Similar quality work is required in other patient groups in order to advance this area of research.

Exercise and cancer prognosis

Much of the research in the area of exercise and oncology has involved relatively short-term interventions with acute outcomes (as described above). However, interest has also been increasing in the role that exercise may play in cancer-related and all-cause mortality among cancer survivors.

A landmark paper published in 2005 was the first large-scale, cohort study to report a significant protective association between physical activity after breast cancer diagnosis and recurrence, cancer-related mortality and overall mortality (Holmes et al, 2005). Breast cancer survivors who participated in 9–14.9 MET/h/wk of physical activity had a 41% risk reduction in total mortality, a 50% risk reduction for breast cancer death, and a 43% risk reduction of breast cancer recurrence compared to those doing <3 MET/h/wk (9 MET/h/wk is equivalent to 3 hours of walking at an average pace per week). Since this publication, a number of other studies have examined associations between pre- or post-diagnosis physical activity and both breast cancer deaths and all-cause mortality. A meta-analysis that summarized the results (Ibrahim and Al-Homaidh, 2010) concluded that any level of physical activity post-diagnosis (>2.8 MET/h/wk) was associated with reduced breast cancer (34%) and all-cause mortality (41%) compared to the reference group. An interesting finding was the lack of a dose response relationship, with similar reductions in mortality seen at all levels of activity above 2.8 MET/h/wk,

although it is possible that this was the result of measurement error because all studies were reliant on self-report. Misperception of what constitutes vigorous intensity activity may have resulted in misreporting of higher activity levels.

While research in this area is also dominated by studies of breast cancer patients, a handful of large prospective studies have also been conducted in colon cancer survivors (Meyerhardt et al, 2006a,b, 2009). In an all-female sample Meyerhardt et al (2006a) reported a 50% reduction in all-cause mortality with >9 MET/h/wk of moderate physical activity but the threshold for a protective effect in cancer-specific mortality was considerably higher: >18 MET/h/wk for a 60% reduction. These results were replicated in a mixed sex sample (Meyerhardt et al, 2006b).

It could be argued that patients who are not physically active after cancer diagnosis develop more aggressive tumours and are more unwell than those who do. In order to control for this, most of the studies have reported a separate analysis excluding patients who died within the first year of follow up, and the results change very little, indicating that the observed protective effect was not an artefact of a healthy selection bias.

A number of plausible biological mechanisms have been suggested to explain the protective effect of physical activity after cancer diagnosis. Among breast cancer survivors, exercise may reduce the availability of oestrogen and increase concentrations of sex hormone binding globulin, both of which are associated with incidence of breast cancer (Missmer et al, 2004). This is supported by results from Holmes et al's (2005) study which found that reductions in breast cancer deaths were only seen in oestrogen receptor-positive tumours. Insulin and insulin-like growth factor have also been associated with mortality in cancer survivors (Goodwin et al, 2002). Insulin and insulin-like growth factor have known mitogenic properties and may therefore stimulate tumour cell proliferation. Exercise can potentially reduce mortality through direct or indirect effects (i.e. as a result of weight loss) on insulin-like growth factor and insulin levels. Reductions in gastrointestinal transit time have also been suggested as a possible mechanism among colon cancer survivors (Harriss et al, 2009), as have changes in prostaglandin levels or ratios. There has also been speculation that adipokines (Jarde et al, 2008) and inflammatory and immune responses may play a role (Campbell and McTiernan, 2007). Currently there is no definitive evidence for the mechanisms through which exercise exerts its protective effect, but it is likely to involve many of these pathways.

At present, the only available data on exercise and prognosis are from observational studies. In order to be confident that a causal association exists methodologically vigorous randomized controlled trials are required. One such study is underway: Courneya and colleagues are conducting a large, multi-site exercise intervention in survivors of stage II and III colon cancer (Courneya et al, 2008). The intervention is delivered over 3 years, with a 4-year follow up and, as such, results will not be available for some time. Similar trials are required among survivors of other cancer sites.

Current recommendations for exercise prescription in cancer survivors

With the growing body of evidence that exercise may have beneficial effects on numerous physiological and psychosocial outcomes in cancer survivors, an obvious question for practitioners is what type of exercise programme they should suggest to their patients. The American College of Sports Medicine convened a roundtable of experts in the field of exercise and cancer survivorship to synthesize current evidence and provide such guidelines (Schmitz et al, 2010). It provides recommendations for medical examination and exercise testing before commencing an exercise programme, with specific reference to survivors of breast, prostate, colon, haematological and gynaecological cancers. Interested readers are referred to the paper which provides a comprehensive summary of cancer-specific considerations both before and during an exercise programme.

In general the guidelines recommend that all exercise programmes should be individualized taking into consideration treatments received and associated symptoms, comorbidities, contraindications to activity, and patient prognosis. Recommendations are in accordance with previously published guidelines from the American Cancer Society and the US Department of Health and Human Services; that is to 'avoid inactivity and return to normal daily activities as soon as possible after surgery and during adjuvant cancer treatments'. In addition, it was agreed that US Department of Health and Human Services guidelines were appropriate for cancer survivors, but should be adapted to the individual. These guidelines are to accumulate 150 minutes of moderate intensity activity per week or 75 minutes of vigorous intensity exercise or an equivalent combination. Two or three sessions of resistance exercise per week including major muscle groups are also advised, along with flexibility exercise on days that other exercise is performed.

Even with clear recommendations, this is a challenging population for which to design exercise programmes given the huge variation in cancer and treatment-related symptoms, late effects and associated comorbidities. Specific training for health professionals interested in providing exercise-based cancer rehabilitation is required and some organizations are beginning to provide such a service. For example, CanRehab (www.canrehab.co.uk) is a UK-based organization providing seminars, workshops and training programmes for exercise-based rehabilitation aimed at health and fitness professionals. In the USA, the American College of Sports Medicine has launched the Cancer Exercise Training Certification and

in addition, the Rocky Mountain Cancer Rehabilitation Institute Program has been running at the University of Northern Colorado for several years.

Conclusions

The evidence to date suggests that exercise is an effective therapy for reducing cancer-related sequelae and potentially reducing disease burden in what is a rapidly growing population. With such a low-cost intervention having the potential to improve the health and wellbeing of this vulnerable group, investment to provide wider access to training and support is urgently needed. **BJHM**

Conflict of interest: none.

Campbell KL, McTiernan A (2007) Exercise and biomakers of cancer prevention. *J Nutr* **137**: (161S) 169S

Cancer Research UK (2009) *Cancer Survival Statistics.* info.cancerresearchuk.org/cancerstats/survival/ (accessed 1 February 2011)

Conn VS, Hafdah, AR, Porock DC, McDaniel R, Nielsen PJ (2006) A meta-analysis of exercise interventions among people treated for cancer. *Support Care Cancer* **14**(7): 699–712

Courneya KS, Friedenreich CM (1999) Physical exercise and quality of life following cancer diagnosis: A literature review. *Ann Behav Med* **21**(2): 171–9

Courneya KS, Booth CM, Gill S et al (2008) The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group. *Curr Oncol* **15**(6): 8–16

Cramp F, Daniel J (2008) Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* (2): 10.1002/14651858.CD006145.pub2

Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM (2005) Riding the crest of the teachable moment: Promoting long-term health after the diagnosis of cancer. *J Clin Oncol* **23**(24): 5814–30

Department of Health (2007) *Cancer Reform Strategy 1.* The Stationery Office, London

Galvao DA, Newton RU (2005) Review of exercise intervention studies in cancer patients. *J Clin Oncol* **23**(4): 899–909

Goodwin PJ, Ennis M, Pritchard KI et al (2002) Fasting insulin and outcome in early-stage breast cancer: Results of a prospective cohort study. *J Clin Oncol* **20**(1): 42–51

Harriss D, Cable T, George K, Reilly T, Renehan A, Haboubi N (2009) Physical activity before and after diagnosis of colorectal cancer. In: Saxton J, Daley A, eds. *Exercise and cancer survivorship: Impact on health outcomes and quality of life.* Springer, London: 153–72

Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA (2005) Physical activity and survival after breast cancer diagnosis. *JAMA* **293**(20): 2479–86

Ibrahim E, Al-Homaidh A (2010) Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. *Med Oncol* doi: 10.1007/s12032-010-9536-x [Epub ahead of print]

Jarde T, Caldefie-Chezet F, Damez M, Mishellany F, Penault-Llorca F, Guillot J, Vasson MP (2008) Leptin and leptin receptor involvement in cancer development: A study on human primary breast carcinoma. *Oncol Rep* **19**(4): 905–11

Jones LW, Peddle CJ, Eves ND et al (2007) Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer* **110**(3): 590–8

Jones LW, Eves ND, Peterson BL et al (2008) Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients a pilot study. *Cancer* **113**(12): 3430–9

Jones LW, Eves ND, Kraus WE et al (2010b) The lung cancer exercise training study: a randomized trial of aerobic training, resistance training, or both in postsurgical lung cancer patients: rationale and design. *BMC Cancer* **10**: 155

Jones LW, Watson D, Herndon JE, Eves ND, Haithcock BE, Loewen G, Kohman L (2010a) Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. *Cancer* **116**(20): 4825–32

Knols R, Aaronson NK, Uebelhart D, Fransen J, Aufdemkampe G (2005) Physical exercise in cancer patients during and after medical treatment: A systematic review of randomized and controlled clinical trials. *J Clin Oncol* **23**(16): 3830–42

Maddams J, Moller H, Devane C (2008) *Cancer Prevalence in the UK, 2008.* www.thames-cancer-reg.org.uk/news/uk_prevalence_14072008.pdf (accessed 21 March 2011)

Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, Fuchs CS (2006a) Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol* **24**(22): 3527–34

Meyerhardt JA, Heseltine D, Niedzwiecki D et al (2006b) Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: Findings from CALGB 89803. *J Clin Oncol* **24**(22): 3535–41

Meyerhardt JA, Giovannucci EL, Ogino S, Kirkner GJ, Chan AT, Willett W, Fuchs CS (2009) Physical activity and male colorectal cancer survival. *Arch Intern Med* **169**(22): 2102–8

Missmer S, Eliassen A, Barbieri R, Hankinson S (2004) Endrogenous estrogen, androgen, and progesterone concentraions and breast cancer risk among post-menopausal women. *J Nat Cancer Inst* **96**: 1856–65

National Cancer Institute (2010) *Fatigue*. www.cancer.gov/cancertopics/pdq/supportivecare/fatigue/patient (accessed 29 March 2010)

National Coalition for Cancer Survivorship (1986) *History & Milestones.* www.canceradvocacy.org/about/org/history.html (accessed 21 March 2011)

Pujol JL, Quantin X, Chakra M (2009) Cardiorespiratory fitness in patients with advanced non-small cell lung cancer why is this feature important to evaluate? Can it be improved? *J Thorac Oncol* **4**(5): 565–7

Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R (2005) Controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* **14**(7): 1588–95

Schmitz KH, Courneya KS, Matthews C et al (2010) American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors. *Med Sci Sports Exerc* **42**(7) 1409–26

Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH (2010) An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* **4**: 87–100

Travis LB (2006) The epidemiology of second primary cancers. *Cancer Epidemiol Biomarkers Prev* **15**(11): 2020–6

Wingo PA, Ries LA, Parker SL, Heath CW (1998) Long-term cancer patient survival in the United States. *Cancer Epidemiol Biomarkers Prev* **7**: 271–82

World Cancer Research Fund/American Institute for Cancer Research (2007) *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.* AICR, Washington DC

KEY POINTS

- Epidemiological studies have consistently shown exercise to have an inverse association with the incidence of numerous cancers, but the role of exercise in the oncology setting is a relatively new area of research.
- Evidence consistently shows exercise to be safe and well tolerated in cancer patients receiving treatment and those who have completed therapy.
- Exercise is associated with improvements in numerous treatment-related symptoms and psychosocial outcomes such as cancer-related fatigue and quality of life.
- Studies show exercise to be associated with reductions in cancer-related and all-cause mortality in breast and colon cancer survivors, with plausible biological mechanisms.
- Cancer survivors are advised to adhere to general population guidelines for exercise.
- More investment is required to provide training and support for health practitioners and fitness professionals to promote exercise in this vulnerable population.