THE CANCER REVOLUTION

Additional Material for Chapter 8

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Prof. Thomas provided us with an extremely generous chapter on exercise that we unfortunately were not able to include in its entirety. Also, to bring the chapter stylistically closer to other material in the book, it was quite significantly edited. Hence we are providing the full, original, unedited chapter here.

Whether we do something about it or not, most of us realise that regular exercise and a healthy lifestyle reduces our risks of developing many serious diseases including cancer – What is less well known are the enormous benefits of exercise after a diagnosis of cancer, not only to reduce the side effects of treatment, improve physical and psychological well-being but to increase the chances of long lasting remission and cure. In many cases, the magnitude of these benefits are on a par with that provided by chemotherapy, yet mainstream oncology units have been slow to offer exercise guidance and support for their patients.

This chapter reviews the evidence from published clinical studies, describes the underlying mechanism of how exercise fights cancer, provides guidance on how, when and how often to exercise and describes systems which would integrate exercise and lifestyle rehabilitation into routine clinical management.

Evidence that physical activity improves well-being after cancer

Through a combination of earlier detection and enhanced treatments, the chance of surviving cancer has significantly improved for its unfortunate victims. For example, the average chance of living 5 years for a woman with breast cancer when I first became a consultant, in 1990, was just 54% now it is 84%. To achieve this and similar benefits for other cancer types, however, patients usually have to endure more complex and arduous therapies which often leave them beleaguered with acute and long term effects which considerable impact on their quality of life.

Fortunately, well conducted clinical studies have demonstrated a significant benefit for exercise as a major factor for reducing the severity of many of these adverse effects. A meta analysis of 34 randomised trials published in the BMJ in 2012 involving patients exercising after cancer, showed a benefit for fatigue, mood, anxiety, depression, muscle power, hand grip, exercise capacity and quality of life [Fong et al 2012]. Other trials have shown that regular exercise during and after cancer treatments reduce the serious risk of blood clots which effects up to 15% and in some can be life threatening. The evidence for the benefits of exercise spans across the common cancer types and following different treatment including surgery, radiotherapy, chemotherapy, hormones, hormones and even the newer biological therapies. The next section of this chapter describes some specific programmes and clinic studies addressing the more common symptoms which plague cancer survivors.

Cancer-related fatigue (CRF)

CRF has overtaken nausea and pain as the most distressing symptom experienced by patients during and after their anti-cancer therapies. It is reported by 60-96% of patients

during chemotherapy, radiotherapy or after surgery. Cancer-related fatigue can have a profound effect on the whole person, physically, emotionally and mentally and can persist for months or even years following completion of treatment [Velthuis et al. 2009]. It is also reported in up to 40% of patients taking long term therapies such as hormone or biological therapies [Wagner & Cella, 2004].

The first step to treating CRF is to correct, if possible, medical conditions which can aggravate it anaemia; drugs such as opiates, antihistamines, and anti-sickness medication; electrolyte imbalance; liver failure; steroid withdrawal sedatives, depression, nocturia, night sweats and pruritis [Thomas et al 2005].

The self-help strategy most extensively investigated for CRF is exercise. There have been two recent meta-analyses addressing CRF and exercise interventions. The first, a Cochrane review published in 2008, reviewed 28 RCT's involving 2083 participants in a variety of exercise programmes and showed that exercise was statistically more effective in reducing CRF than the control, although the benefit overall was small [Cramp & Daniel, 2008]. and the second, in 2009, from the Netherlands, reviewed 18 RCT's involving 1109 participants [Velthuis et al 2009].

This meta-analysis subdivided the data into two main exercise strategies: 1) home-based programmes, involves giving patient's advice to exercise, unsupervised in their own home; 2) referring patients to a supervised exercise programme including a combination of aerobic and resistance exercises. More of the studies involving supervised aerobic exercise programmes reached significance and the degree of improvement was better than the home-based programmes.

Weight gain and body composition

Weight gain during and after adjuvant chemotherapy is becoming an ever-increasing significant concern. Women with breast cancer, for example, report a 45% incidence of significant weight gain, often at a time in their lives that makes losing it difficult. In men a study of 440 prostate cancer survivors reported that over 53% were overweight or obese [Thomas et al 2012]. For individuals 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 et al. 2008]. The reasons for this are multifactorial, some patients concerned about weight loss, perhaps from dated and misleading information sources and tend to overeat; others, with fatigue and nausea, stop exercising, and drugs, including steroids and hormone therapies such as tamoxifen and LHRH agonists. Whatever the reasons for weight gain, numerous reviews and meta analysis of the published literature have demonstrated that individuals who gain weight after cancer treatments have worse survival and more complications [Knols R, 2005]. Fortunately, supervised exercise programmes have been shown to improve weight and have significant other benefits on body constitution and fitness such a lean mass indices, bone mineral density, cardiopulmonary function, muscle strength and walking distance [Knols R, 2005].

Psychological well-being

Understandably, being diagnosed with cancer is a stressful experience and requires a high level of emotional and social readjustment. Whilst many people adjust well to a cancer diagnosis, prevalence rates of 25-30% for psychological distress are consistently reported [Drouin et al 2005]. Still, psychological wellbeing, such as mood status, depression and anxiety are under-diagnosed in up to 50% of cases [Knols, 2005]. As well as being distressing for the patient and carers, cohort studies have also suggested that depressed patients, for example, with lung and breast cancer have reduced survival

compared to those who are psychologically healthy (Kadan-Lottick, 2005). A number of observational studies among patients receiving therapies ranging from chemotherapy, radiotherapy and hormone therapies have demonstrated reduced levels of depression, anxiety and improved quality of life, improved mood, happiness, self-esteem especially if they involve group activities [Mock, 2001].

Overall quality of life

Regular exercise has been shown to improve quality at all stages of illness and for several different types of cancer. For example, in a study involving 1,966 patients with colorectal examined, those achieving at least 150-minutes of physical activity per week had an 18% higher QoL score than those who reported no physical activity, measured by the QoL (FACT-C) [Lynch et al. (2008]. Another study showed similar benefits in relation to exercise in a RCT of 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 et al 2003]. Another RCT compared supervised resistance exercise versus control in 135 men with prostate cancer who were scheduled to receive androgen deprivation therapy for at least 3 months. There was a significant improvement in QoL outcomes in the intervention group and a significant decline in the control group [Segal et al 2003].

Bone health (osteoporosis)

Pre-menopausal women who have had breast cancer treatment are at increased risk for osteoporosis and fracture due to reduced levels of oestrogen, brought on by a premature menopause caused by chemotherapy, surgery or hormones. Men who receive hormone deprivation therapy for prostate cancer have an increased risk of developing osteoporosis. Post-menopausal women are at a higher risk if they receive aromatase inhibitors [Thomas et al 2004]. Osteopenia, osteoporosis and increased rates of fracture have also been noted in survivors of many other cancers, including testicular, thyroid, gastric and CNS cancers, as well as non-Hodgkin's lymphoma and various haematological malignant diseases [Brown et al 2003]. Medical conditions which are associated with a higher risk of osteopenia include thyroid disorders, prolonged warfarin and corticosteroid intake. Lifestyle factors which increase the risk factors for developing osteoporosis include a low calcium intake, low protein diet, lack of physical activity, smoking, and excessive alcohol intake [Mackey & Joy 2005]. A number of well conducted retrospective and RCT studies have identified exercise as an intervention to reduce the risk of done mineral loss [Brown et al 2003, Mackey & Joy 2005 ref].

Summary learning points

- Regular light exercise reduces cancer related fatigue
- Too much intense exercise can make fatigue worse
- Supervised exercise regimens have the best results for reducing fatigue
- Exercise programmes improve psychological well being
- Group and socially interactive programmes have the best result for mood and anxiety
- Regular exercise reduces the risk of thromboembolism during chemotherapy
- Regular exercise during cancer treatments prevents weight gain
- Regular exercise helps individuals loose weight after cancer treatments
- The best weight control programmes combine exercise with a healthy calorie reducing diet
- Weight barring exercise is better to prevent bone loss

- Non- weight barrier exercise still helps prevent bone loss
- Exercise has to be kept going for several months before a benefit is seen

Evidence that physical activity reduces relapse rates and improves overall survival

One of the best studies to provide evidence of a survival benefit comes from an RCT published in 2005 where 2,437 postmenopausal women with early breast cancer were randomised to nutritional and exercise counselling, or not, as part of routine follow-ups [Chlebowski RT et al]. The dietary and exercise intervention included eight bi-weekly individual counselling sessions. Dietary fat intake reduction was significantly greater weight was lower and less women relapsed with breast cancer and overall survival was greater in the intervention group. Another RCT published in 2005 randomised 98 men with early prostate cancer to an exercise and lifestyle intervention or standard follow active surveillance. The average PSA in the intervention group went down and in the control group it went up (Statistically significant 10% difference). The researchers also added the serum of participants to the androgen dependent prostate cancer cells grown in a petri dish. The individuals who exercised the most had the greatest reduction in cell growth with even greater statistical significance [Ornish et al] .

A further prospective study published in 2007 reported that over a third of men who changed their lifestyle after prostate cancer had a slowing or halting of their PSA progression [Thomas et al 2007]. Further evidence will be gained in another large national 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 [www.pomi-T.com]

Most of the other evidence for a reduced relapse rate and improved survival after cancer come from retrospective analysis of prospective cohort studies. The most notable are summarised below.

- 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.
- Haydon et al. (2006) retrospectively analysied a RCT involving patients with stage III bowel cancer and found had a significant association between exercise and a 31% reduction in relapse rate.
- Meyerhardt et al (2005) found in a similar analysis of patients with bowel cancer found a 35% reduction in relapse rate in physically active patients after chemotherapy.
- Kenfield et al (2012) performed a subset analysis of 2,686 men with prostate cancer within the large Health Professionals Follow-up Study. Men who were physically active, especially those engaging in >3 MET-hours of total activity, had a 35% lower risk of overall death.

These studies as well as others not mentioned here have been reviewed by The National Cancer Institute in a recent meta-analyis. Amoung 45 observational studies and RCT's the strongest evidence was demonstrated for breast cancer survivors, The next strongest evidence was for colorectal cancer survivors [Rachel Ballard-Barbash et al 2012].

What type and how much to exercise do we need to do

In terms of improved well being and reducing side effects, the best results appear to be with programmes which had a combination of aerobic and anaerobic exercise particularly within a social group. Studies have demonstrated benefits with gym exercises, Medical Qigong (MQ), Tai Chi Chuan or dances including Celtic, American, Jazz, Afro-Cuban, Reggae, Middle Eastern and Cajun. The precise amount of exercise has to be determined on an individual basis and the limit to the amount of exercise depends on a number of factors including pre-treatment ability, current disability caused by the cancer itself, surgery, radiotherapy or chemotherapy and time proximity to major treatments. An exercise programme supervised by a trained professional has major advantages. They can design a bespoke regimen which starts slowly then build up to an acceptable and enjoyable pace. They can help motivate the individual to continue exercising for the short and long term. They can judge the optimal exercise levels to improve fatigue and not aggravate it.

In terms of exercise to reduce a cancer relapse most of the cohort studies summarised above suggest a figure of moderate exercise of around 2.5 to 3 hours a week for breast cancer but men continued to have a benefit for prostate cancer mortality if they walked over 4 or more hours per week. In addition, compared to men who walked less than 90 minutes at an easy walking pace, those who walked 90 or more minutes at a normal to very brisk pace had a 51% lower risk of all-cause mortality. More vigorous activity, and longer duration of activity, was associated with significant further reductions in risk for all-cause mortality [Kenfield et al 2012]. In a separate study, of 1,455 men with prostate cancer researchers found that a walking at a pace of at least 3 miles/hour for 3 hours or more per week gave a 57% less likely to develop PSA relapse compared to men who walked less than 3 miles/hour [Richman et al 2011].

The underlying mechanisms of an anti-cancer effect of exercise

The randomised study by Ornish et al, mentioned above, eloquently demonstrated that the chemical environment of the blood improves for the better after exercise and a healthy lifestyle. Blood from exercisers resulted in a real change in cancer cell growth in a petri dish. The precise chemicals which are responsible for the anti-cancer mechanisms remain unconfirmed but several contenders have been postulated and these are summarised below:

Vasoactive Intestinal Protein (VIP) drives cancer cells to grow faster and spread. Sedentary breast and prostate patient's have higher VIP titres compared to individuals who regularly exercise who have increased production of natural anti-VIP antibodies [Velijkovic et al 2012].

Gene expression: A study involving men with prostate cancer showed that over 180 genes were expressed more favourably in tumours from men who jogged, played tennis or swam for > 3 hrs/wk, compared with sedentary men [Kenfield et al 2011].

Insulin-like growth factors (IGF); 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 [Kaaks et al.2000]. An inverse relationship with insulin like growth factor binding protein 3 (IGFBP-3) levels has also been shown, although this effect has not been

confirmed in all studies (Palmqvist et al 2002; Ma et al1999]. The benefits of lowering IGF-1 may be linked to its central role in growth regulation processes. The main stimulus for IGF-1 production comes from growth hormone (Kaaks et al 2002). This stimulatory effect of growth hormone is modulated by insulin, which increases growth hormone receptor levels and in turn IGF-1 (Baxter & Turtle 1978]. Early studies have shown that after binding to it's receptors, which are found on normal colonic mucosal cells as well as colon cancer cells, IGF-1 can stimulate cell proliferation, inhibit apoptosis [Yu & Rohan 2000], and promote angiogenesis [Freier et al., 1999]. In the circulation, as over 90% of IGF-1 is bound to IGFBP-3, binding inhibits the action of IGF-1 by limiting the availability of free hormone. The most convincing clinical evidence comes from a large 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].

Oestrodiol levels; Serum estradiol and free estradiol is lower amoung exercisers compared with the controls even after adjusting for weight lost [Friedenreich et al 2009]

Other direct effects – Exercise has been shown to enhance P53 activity who's function is to slows down the cell cycle and encourage apoptosis if partial damage has occurred thus preventing the cell mutating to a cancerous form. Other studies have demonstrated prostaglandin and COX-2 inhibition which have positive effects on the immune system [Chaudry et al 1994].

Indirect effects: Exercise helps weight reduction – Obese individuals have higher Leptin levels, a neuropeptide cytokine which has cancer promoting properties [Surmacz et al 2007]. Adiposity also influences the production and availability of the body's sex hormones including oestrogen, androgens and progesterone. In post-menopausal women, oestrogen is made in the peripheral body fat whilst in pre-menopausal women it is produced primarily in the ovary. This may explain a higher risk of breast and endometrial cancers for overweight, post-menopausal women, but not pre-menopausal women. Fortunately, oestrogen levels have been shown to reduce, following weight reduction programmes. Exercise and diet help to control the body's levels of serum lipids and cholesterol; high levels of these fats have been particularly associated with greater risk of advanced, higher grade disease at presentation [Harvei et al].

How to incorporate exercise into mainstream cancer management

Various pilot schemes have been started throughout the UK which have varing degrees of success. The problem with these 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 [Jolliffe et al 2000]. This would involve a hospital scheme run by physiotherapist or occupational therapist to supervise patients immediately after surgery, radiotherapy and even during chemotherapy then refer on to a community based scheme for the long term. Unfortunately, this would be expensive and in these times of austerity unlikely to be funded. Instead we have to look into expanding existing services with minimum investment. The National Exercise Referral Scheme already exists for other chronic conditions such as obesity, lower back pain, within a network of over 5,500 gyms in the UK. Professor Thomas backed by Macmillan Cancer Relief successfully campaigned and wrote the national standards for the scheme to be expanded to include cancer rehabilitation and these were accepted in 2010. Charities such as The Wright Foundation

have now developed training courses for exercise professionals set against these standards [www.wrightfoundation.com]. The course empowers trainers to be more confident in helping cancer survivors to exercise by providing an insight to its treatment, how treatments effect the ability to exercise and practical issues such as dealing with a stoma, altered body image, peripheral neuropathy, hand foot syndrome , dry eyes and fatigue. If successful, trainers gain a Register of Exercise Professional (REPS) level four qualificaton which allows them to receive referrals from GP's and other health professional.

This referral scheme has been up and running in North Bedfordshire since 2010 and uptake with post referral follow up motivational telephone calles is over 65% [Thomas et al 2010] The challenge now is to expand the scheme, nationally so in order to provide the evidence for the department of Health, the Primrose Lifestyle Clinical Research unit are now conducting a randomised controlled trial to establish the benefits, feasibility and cost-effectiveness of expanding this scheme nationally.

In addition, to the gym referral scheme there are many other exercise groups such as walking, dance, swimming, golf and piliates which may be better suited than the gym for many individuals. The patient information and lifestyle website (cancernet.co.uk/exercise.htm) has established an exercise potal which explains why , how and when to exercise. It has a search facility for avaialble exercise groups providing addresess contact details and times of classes via post code location. In addition the Macmillan cancer relief exercise expert advisory committee is conducting a media campaign to raise public awareness and have designed helpful writen and web based patient information materials as part of its Move More programme.

Conclusion

There are a wealth of well conducted studies which have demonstrated association between regular exercise and lower risk of complications and troublesome side effects after cancer and its treatments. Accepting the caveats of retrospective data there is also little doubt that exercisers have a lower relapse rate and have a better overall survival. The fact that several large trials all show a similar level of exercise is very convincing but there remain some concerns that this may be a cause and effect phenomenon as there are several overlapping lifestyle factors which may contribute to a lower relapse rate - exercisers may just do better because they are fitter going into cancer treatments and less likely to be over weight, have better diets and do not smoke. Although the existing RCT's provide encouraging evidence that exercise intervention programmes are beneficial further large RCT are needed, particularly in terms of cost effectiveness before commissioners start investing particularly in the area.