

Diet, physical activity and energy balance and their impact on breast and prostate cancers

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Obesity, physical activity status and circulating levels of sex steroid hormones and growth factor proteins are intrinsically linked to energy balance. Epidemiological studies have previously reported associations between these factors and the risk of hormone-related cancers such as prostate and breast cancer in men and postmenopausal women. An increasing number of intervention studies in 'at-risk' populations and cancer survivors are now investigating the effects of lifestyle interventions that promote negative energy balance on circulating levels of sex hormones and growth factor proteins as surrogate markers of cancer risk. Evidence from these studies suggests that lifestyle interventions can improve insulin sensitivity, alter the balance of circulating sex steroid hormones and insulin-like growth factor (IGF) axis proteins (including IGF-1 and the IGF binding proteins 1 and 3) and change the functioning of immune cells in peripheral blood. Such changes could influence the risk of developing hormone-related cancers, as well as having the potential to improve disease-free survival in patients recovering from cancer treatment. However, despite promising results, the methodological quality of most intervention studies has been limited due to small subject numbers, lack of adequate control groups or non-randomised designs and the absence of long-term follow-up measures. More intervention studies with randomised controlled designs, higher numbers of subjects and longer-term follow-up measures are needed to establish which combination of specific dietary and physical activity interventions work best for reducing risk in 'at-risk' populations and survivors, optimal dose–response relationships and the magnitude of change in surrogate markers of cancer risk that is required to induce a protective effect.

Lifestyle interventions: Negative energy balance: Diet and exercise: Hormone-related cancers

Introduction

In the UK, cancers of the breast and prostate represent the most prevalent forms of the disease in women and men, respectively. More than 40 000 new cases of breast cancer were diagnosed in 2001, which accounts for 30% of all female cancers and almost half (48%) of all cancers diagnosed in UK women aged 40–60 years (Cancer Research UK, 2005a). Prostate cancer accounted for 22% of all male cancers in 2001, with over 30 000 new cases (Cancer Research UK, 2005a). Worldwide, breast cancer was estimated to account for 1 105 000 cases and 373 000 deaths in 2000, with the corresponding figures for prostate cancer being 543 000 cases and 204 000 deaths (Parkin *et al.* 2001).

Studies of Scandinavian twins led to estimates that over 70% of breast cancer cases and over 50% of prostate cancer cases are related to environmental factors (Lichtenstein *et al.*

2000). Additional evidence of the role of environmental factors in cancer risk has come from international comparisons, which have reported considerable variation in the incidence of these diseases between countries. For example, the breast cancer incidence is about five times higher in Western countries than in less developed countries and Japan, and mortality from prostate cancer is ten times higher in North America and Europe than Asia (Key *et al.* 2004). However, exposure to Western lifestyles increases the risk of developing both hormone-related cancers in Asian women and men who migrate to the USA (Haenszel & Kurihara, 1968; Ziegler *et al.* 1993).

Evidence suggests that the interaction between Western diets and increased levels of obesity, physical inactivity and insulin resistance might be implicated in the risk of hormone-related cancers such as breast and prostate cancer (Stoll, 1999; Barnard *et al.* 2002). Insulin resistance, and

Abbreviations: DHEA, dehydroepiandrosterone; DHT, 5 α -dihydrotestosterone; 3 α -diol G, 3 α -androstane-3 α ,17 β -diol glucuronide; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; NK, natural killer; PSA, prostate-specific antigen; SHBG, sex hormone-binding globulin.

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the consequent rise in circulating insulin levels, is associated with the consumption of high-fat, refined-sugar diets with excess energy, and overweight individuals, especially with increased intra-abdominal body fat (central adiposity), are at increased risk of hyperinsulinaemia (Matsuzawa *et al.* 1995). However, lifestyle interventions that promote negative energy balance have the potential to improve insulin resistance and influence circulating levels of sex steroid hormones and growth factor proteins that have been linked to the risk of developing hormone-related cancers (Friedenreich & Orenstein, 2002; Barnard & Aronson, 2005).

The main aim of the present review is to consider the evidence linking the risk of hormone-related cancers with lifestyle factors associated with energy balance. A literature search (Medline; National Library of Medicine, Bethesda, MD, USA) was undertaken to find research articles that had (i) investigated associations between lifestyle factors and cancer risk, and (ii) studied the effects of lifestyle interventions on circulating biomarkers implicated in the development of these diseases in 'at-risk' populations. In addition, since lifestyle factors that can affect the risk of developing primary cancers might also be of relevance to the prevention of disease recurrence and secondary primary tumours in cancer survivors, the search was extended to studies of patients recovering from cancer treatment.

Overweight, obesity and risk of hormone-related cancers

Being overweight or obese has been associated with a reduced risk of breast cancer in the premenopausal years (McTiernan, 2003), although a loss of at least 4.5 kg of body weight between the ages of 18 and 30 years was recently reported to halve the risk of developing breast cancer between the age of 30 and 49 years (Kotsopoulos *et al.* 2005). In postmenopausal women, being overweight or obese is associated with a 30–50% increased risk of developing breast cancer (for a review, see McTiernan, 2003), though the role of central adiposity in breast cancer risk is more equivocal (Harvie *et al.* 2003). In addition, a positive association between the risk of oestrogen receptor positive/progesterone receptor positive (ER+/PR+) but not ER-/PR- breast cancer and BMI was reported for postmenopausal women (Enger *et al.* 2000), suggesting a hormone-mediated mechanism. Up to 60% of women diagnosed with breast cancer experience an increase in body weight associated with chemotherapy and treatment-related menopause (Holmes & Kroenke, 2004) and there is evidence that heavier women and women who gain weight after diagnosis have a poorer prognosis and an increased risk of disease recurrence and death compared with normal-weight women, irrespective of menopausal status (Kroenke *et al.* 2005).

The association between obesity and prostate cancer risk seems less clear, with studies reporting a positive association between BMI and prostate cancer risk, no association and even decreased risk in men under 60 years of age, or those with a family history of prostate cancer (for a review, see Freedland & Aronson, 2005). The recent inverse association that has been reported between BMI and prostate cancer risk (Giovannucci *et al.* 2003) is particularly intriguing, as obesity is characterised by lower circulating

testosterone levels in men (Field *et al.* 1994) which could provide a mechanistic link. However, a recent case-control study showed that high visceral fat area and high visceral fat:subcutaneous fat ratio (as quantified by computer tomography) is associated with a more than four-fold increased risk of prostate cancer (von Hafe *et al.* 2004). There is also a growing body of evidence which shows that obesity is an independent predictor of prostate cancer recurrence, adverse pathological features and biochemical progression in prostate cancer patients following treatment with radical prostatectomy (Bassett *et al.* 2005; Freedland *et al.* 2005).

Physical activity and risk of common hormone-related cancers

Prospective epidemiological studies have shown that physical fitness is a strong predictor of cancer mortality in men but not women, with men in the highest physical fitness category having significantly lower risk of cancer mortality in comparison with their sedentary counterparts (Kampert *et al.* 1996; Evenson *et al.* 2003). However, epidemiological evidence of an inverse relationship between physical activity level and risk of hormone-related cancers has been more consistent for breast cancer than for prostate cancer. A comprehensive review of the literature by Gammon *et al.* (1998) showed that eighteen out of twenty-five studies reported a decreased risk of breast cancer among women who were most active at work (risk reduction of 18–52%) or during their leisure time (risk reduction of 12–60%) in comparison with sedentary women, although a dose-response relationship was not evident in most of the studies (Gammon *et al.* 1998). It was unclear whether all physically active women are at decreased risk, or whether the risk reduction is restricted to premenopausal or postmenopausal women only. Furthermore, the wide variety of study designs (including prospective and case-control studies) and problems associated with accurately assessing physical activity status contributed to the conflicting findings on the optimal time period, duration, frequency, or intensity of physical activity required to minimise breast cancer risk. For prostate cancer, the evidence is more inconsistent, with about half of the prospective cohort and case-control studies so far completed reporting a reduction in risk in the range of 10–30% for the most physically active men, but with an increased risk of prostate cancer being observed among the most physically active men in some studies (Thune & Furberg, 2001; Friedenreich & Orenstein, 2002).

Recent evidence has shown that women who have been treated for breast cancer can improve their chances of survival by engaging in a physically active lifestyle (Holmes *et al.* 2005). Compared with women who were least physically active, the risk of death over an average of 8 years of follow-up was halved in breast cancer patients who reported participating in the equivalent of 3–5 h of walking exercise per week at average pace. The benefit of physical activity was particularly apparent in women whose tumours were over-expressing oestrogen and progesterone receptors, consistent with a hormone-mediated mechanism. No detrimental effects of vigorous physical activity

participation were found, but neither was there any evidence that higher weekly energy expenditures were associated with increased benefit (Holmes *et al.* 2005). No epidemiological studies have investigated the effects of physical activity on disease-free survival in patients recovering from prostate cancer treatment.

Lifestyle change and cancer risk: the role of sex steroid hormones and insulin-like growth factor axis proteins

Since circulating sex steroid hormones and growth factors can be influenced by lifestyle factors such as diet, physical activity level and BMI (Friedenreich & Orenstein, 2002; Barnard & Aronson, 2005), an increasing number of intervention studies are investigating how lifestyle changes that promote negative energy balance could affect the risk of hormone-related cancers by modulating circulating levels of sex steroid hormones and insulin-like growth factor (IGF) axis proteins. Intervention studies have focused on the effects of increased physical activity levels, dietary fat restriction and combined exercise and dietary interventions. Consumption of low-fat diets is associated with reduced energy intake in comparison with diets with higher fat content (Lissner *et al.* 1987). However, the independent effects of dietary fat restriction and other changes to the quality of the diet, including fibre intake, cannot be overlooked even though the link between dietary fat consumption and risk of hormone-related cancers is unproven (Schuurman *et al.* 1999; Chan *et al.* 2001; Michaud *et al.* 2001; Smith-Warner *et al.* 2001).

Sex steroid hormones and risk of hormone-related cancers

Breast cancer

The three principal forms of oestrogen in the human body are oestrone, oestradiol and oestriol. In premenopausal women, most oestrogen is produced in the ovaries, with a smaller quantity being produced in the adrenal glands and peripheral tissues (including adipose tissue, the liver and kidneys). After the menopause, ovarian oestrogen synthesis is negligible but oestrogens continue to be synthesised, mainly in the stromal cell fraction of subcutaneous adipose tissue via aromatase activity (Simpson *et al.* 1989). Oestradiol is the primary circulating oestrogen before the menopause, whereas oestrone produced from the peripheral conversion of adrenal androstenedione via aromatase activity in subcutaneous adipose tissue becomes the dominant oestrogen in postmenopausal women (Schindler *et al.* 1972).

Breast cancer risk is increased by early menarche and late menopause (Kelsey, 1979), suggesting an association with premenopausal cyclic ovarian function and duration of oestrogen and progesterone exposure. Oestradiol stimulates breast cell mitosis and evidence suggests that this effect is augmented by progesterone during the luteal phase of the menstrual cycle (Key, 1999). In addition, some breast cancer cell lines are oestrogen dependent (Pike *et al.* 1993), with about two-thirds of these tumours expressing higher concentrations of oestrogen receptor than normal breast

tissues (Early Breast Cancer Trialists' Collaborative Group, 1998), whereas anti-oestrogens such as tamoxifen and ovariectomy inhibit hormone-dependent breast cancer growth (Bulbrook *et al.* 1958; Bagga *et al.* 1995).

Although cumulative lifetime exposure to sex steroid hormones such as oestrogen is considered to increase breast cancer risk, there is no convincing epidemiological evidence of a positive association between increased circulating levels of oestradiol and breast cancer risk in premenopausal women, but results may be confounded by variations in endogenous hormone levels. Of four prospective studies in premenopausal women, two small-scale studies showed no effect and two slightly larger-scale studies showed non-significant trends for higher oestradiol concentrations to be positively correlated with breast cancer risk (for a review, see Key, 1999). However, non-protein-bound (bioavailable) oestradiol is increased in premenopausal breast cancer patients and this is not due to a decrease in circulating sex hormone-binding globulin (SHBG) (Moore *et al.* 1982), which limits the bioavailability of sex steroid hormones in the circulation. More consistent evidence of a link between circulating oestrogens and breast cancer risk exists for postmenopausal women. A recent meta-analysis of nine prospective studies (Key *et al.* 2002) showed that circulating levels of oestrogens, androgens and their precursors are directly related to breast cancer risk in postmenopausal women. Postmenopausal women in the highest quintile of circulating sex hormones had at least a two-fold increased risk of breast cancer compared with women in the lowest quintile. This was true for circulating levels of total and free oestradiol, oestrone, oestrone sulfate, androstenedione, dehydroepiandrosterone (DHEA) and testosterone. The oestrone sulfate:oestrone ratio has also been inversely associated with breast cancer risk in postmenopausal women (Dorgan *et al.* 1996b).

The potential adverse effect of obesity on levels of circulating tumour-promoting sex steroid hormones is likely to underpin most of the increased risk of breast cancer in overweight or obese postmenopausal women. The amount of oestrogen produced from adrenal androstenedione in subcutaneous adipose tissue via aromatase activity and the proportion of oestradiol that is bioavailable (as opposed to protein-bound) is increased in obese *v.* leaner postmenopausal women (MacDonald *et al.* 1978). Furthermore, higher circulating concentrations of oestrone, oestradiol and testosterone, as well as lower circulating levels of SHBG have been reported in obese *v.* leaner postmenopausal women and breast cancer survivors (Verkasalo *et al.* 2001; McTiernan *et al.* 2003). A number of other studies have reported a negative correlation between SHBG and total body fat mass, subcutaneous and intra-abdominal fat and BMI in both premenopausal and postmenopausal women (Haffner *et al.* 1991; Turcato *et al.* 1997; Tchernof *et al.* 1999). Because SHBG serves as a carrier for oestrogen and regulates bioavailability, increased adiposity could be associated with an increase in bioavailable oestrogen.

Prostate cancer

Prostate growth and maintenance depend on androgens such as testosterone (the principal circulating androgen in adult

males) and 5 α -dihydrotestosterone (DHT), the primary androgen in the prostate gland and most potent androgen (Hsing *et al.* 2002). The largest proportion of DHT (65–75%) arises from the conversion of testosterone in peripheral tissue in a reaction catalysed by the enzyme 5 α -reductase or from inactive forms of circulating androgens such as androstenedione, DHEA and DHEA sulfate (Hsing *et al.* 2002). Serum concentration of 3 α -androstane diol glucuronide (3 α -diol G), the main metabolite of DHT, is commonly used as an index of steroid 5 α -reductase activity in the prostate gland, or more generally, intraprostatic androgenicity (Gann *et al.* 1996). Evidence suggests that this predominantly reflects type 2 5 α -reductase which predominates in the prostate gland, because serum levels of DHT and 3 α -diol G decrease in a similar fashion in men treated with the 5 α -reductase type 2 inhibitor, finasteride (Stanczyk *et al.* 1996). The serum testosterone:DHT ratio has also been used as an index of steroid 5 α -reductase type 2 activity (Hsing & Comstock, 1993; Nomura *et al.* 1996).

A meta-analysis of prospective cohort or nested case-control studies showed that men who were in the highest quartile for circulating testosterone level were 2.34 times as likely to develop prostate cancer than those in the lowest quartile (Shaneyfelt *et al.* 2000). Administration of testosterone induces prostate tumours in laboratory animals, whereas prostate cancer regresses after androgen ablation or anti-androgen therapy. Evidence suggests that androgens increase the expression, bioavailability and activity of IGF axis proteins and their receptors, which could have important implications for prostate cancer risk (Chokkalingam *et al.* 2001). In a Chinese population-based case-control study, adjustment for 3 α -diol G and SHBG increased the magnitude of association between prostate cancer risk and serum or plasma IGF-1 levels, and the relationship between IGF-1 levels and prostate cancer risk was significantly more pronounced among men with higher 3 α -diol G levels, suggesting a significant interaction (Chokkalingam *et al.* 2001). In addition, animal studies have shown that induction of prostate tumours by administration of testosterone is enhanced by the addition of oestradiol (Shirai *et al.* 1994), suggesting oestrogens at physiological levels can also enhance prostate carcinogenesis.

The urinary products of oestrogen metabolism, 16 α -hydroxyoestrone and 2-hydroxyoestrone, resulting from the hydroxylation of the parent oestrogens (oestradiol and oestrone), have also been studied in relation to prostate cancer in elderly men. 16 α -Hydroxyoestrone is oestrogenic whereas 2-hydroxyoestrone can act as an oestrogen antagonist (Pasagian-Macaulay *et al.* 1996). Urinary 2-hydroxyoestrone concentration was recently shown to be negatively related to circulating prostate-specific antigen (PSA) levels in older African-American men, with a reduction of 14.2% for each 1.0 ng/ml increase in circulating PSA concentration (Teas *et al.* 2005). However, an increase in urinary 2-hydroxyoestrone clearance was also observed in older men with high BMI (>30 kg/m²), suggesting dysregulation of this oestrogen metabolism pathway (Teas *et al.* 2005). BMI has been reported to be positively correlated with prostate volume in black and

white Caucasian men (Daniell, 1993; Soygur *et al.* 1996; Sarma *et al.* 2002), which could be linked to increased oestradiol and oestrone levels in obese men through the transformation of adrenal androstenedione via aromatase activity in subcutaneous adipose tissue (Sarma *et al.* 2002). Aromatase activity accounts for a large proportion of oestradiol and oestrone production in men and increases with obesity and age (Kley *et al.* 1980). However, the association between BMI and prostate volume in black men observed by Sarma *et al.* (2002) was independent of oestrogen or testosterone levels (Sarma *et al.* 2002). Although there is limited research in this area, further studies of oestrogen metabolism, its links to prostate cancer risk, and the possible modulating effects of obesity and lifestyle interventions in middle-aged men at increased risk are warranted.

Reduced dietary fat, physical activity and circulating sex steroid hormones

A meta-analysis of dietary fat intervention studies, in which percentage energy from fat intake was changed to 18–25% in eleven studies and 10–12% in two studies, showed that reduced dietary fat intake was associated with decreases in serum oestradiol of 7.4% in premenopausal women (measured at various points of the menstrual cycle) and 23% in postmenopausal women (Wu *et al.* 1999). In premenopausal women, postmenopausal women and postmenopausal breast cancer survivors, decreases in circulating oestrone and oestrone sulfate and oestradiol have all been observed following short-term low-fat dietary interventions in which the total energy intake from fat was restricted to 10–25% from 3 weeks to 6 months duration (Rose *et al.* 1987, 1992, 1993; Boyar *et al.* 1988; Woods *et al.* 1989, 1996; Heber *et al.* 1991; Goldin *et al.* 1994). However, in these populations, there is also evidence that SHBG decreases in response to low-fat diets or moderate restriction of energy intake (Rose *et al.* 1993; Goldin *et al.* 1994; Crave *et al.* 1995; Woods *et al.* 1996), potentially increasing sex steroid hormone bioavailability, although more severe short-term restriction of energy intake (1380 kJ (330 kcal)/d) increases circulating SHBG levels (Franks *et al.* 1991).

In postmenopausal breast cancer survivors, some recent preliminary evidence shows that eating a low-fat diet could significantly improve relapse-free survival. Women who reduced their dietary fat intake to 20% of the total energy were compared with a control group eating a standard diet containing a higher proportion of fat. After 5 years, breast cancer had recurred in 9.8% of the women in the intervention group in comparison with 12.4% in the controls but the dietary effect appeared to be greater in women with hormone receptor-negative disease (Chlebowski *et al.* 2005). This suggests that the apparent protective effect of the lower-fat diet was not associated with a hormone-mediated mechanism. These preliminary data did not control for fruit and vegetable consumption, chemotherapy treatment or the effects of weight loss, which averaged nearly 2 kg in the intervention group.

In middle-aged men, change from a high-fat, low-fibre diet to a low-fat, high-fibre diet over a period of 8 weeks resulted in a decrease in circulating testosterone and adrenal

androgens (androstenedione and DHEA), and smaller decreases in circulating concentrations of oestradiol and SHBG without altering urinary clearance (Wang *et al.* 2005). A decrease in circulating total testosterone and SHBG-bound testosterone has also been reported in men aged 19–56 years after changing from a high-fat, low-fibre diet to a low-fat, high-fibre diet (Dorgan *et al.* 1996a).

Participation in physical activity is reported to be associated with changes in menstrual cycle duration and circulating oestrogens that could potentially influence breast cancer risk. In premenopausal women, regular exercise is associated with longer menstrual cycles which might be due to suppressed release of gonadotrophin-releasing hormone (Walberg-Rankin *et al.* 1992; Cooper *et al.* 1996) and can delay the onset of the menstrual cycle in adolescent females or cause anovulation so that exposure to oestrogen and progesterone is reduced or delayed (Bernstein *et al.* 1987; Merzenich *et al.* 1993). In postmenopausal women, increased levels of physical activity were reported to be associated with decreased serum concentrations of oestrone (but not oestradiol or testosterone) (Nelson *et al.* 1988), whereas 4–5 months of moderate-intensity physical exercise resulted in decreased circulating levels of SHBG (Caballero & Maynar, 1992; Caballero *et al.* 1996), which could act to increase sex steroid hormone bioavailability.

There is limited evidence from short-term combined programmes of exercise and low-fat diets in premenopausal or postmenopausal women or in middle-aged men. However, in a study of postmenopausal women following a low-fat (10% of total energy) high-fibre (8.4–9.6 g dietary fibre/100 kJ (35–40 g dietary fibre/1000 kcal) per d) complex-carbohydrate diet combined with exercise (walking exercise 6–7 d/week), serum insulin was decreased by 39 and 19% in those taking and not taking hormone replacement therapy, respectively, and was associated with corresponding increases in SHBG of 39 and 42% in the two groups, which could decrease sex steroid hormone bioavailability (Tymchuk *et al.* 2000). However, a small feasibility study, involving ten breast cancer survivors who were mainly postmenopausal, only reported slight non-significant changes in free oestradiol, oestrone sulfate, total testosterone, androstenedione and DHEA after a combined 8-week low-fat (20% of total energy) and aerobic exercise intervention (McTiernan *et al.* 1998a) in which a moderate 1.2 kg loss of body weight was also observed (Table 1). In middle-aged men following a combined 3-week intensive low-fat-diet (10% fat; 10–15% protein; 75–80% high-complex carbohydrate) and exercise intervention (daily walking and supervised exercise), serum oestradiol was halved but without change in serum testosterone levels (Rosenthal *et al.* 1985). In another study by the same group (Tymchuk *et al.* 1998), an increase in serum SHBG was accompanied by a decrease in fasting insulin in middle-aged men following the same intervention (Table 1).

The urinary products of oestrogen metabolism, 16 α -hydroxyoestrone and 2-hydroxyoestrone, have also been studied in relation to breast cancer risk and lifestyle interventions associated with negative energy balance in premenopausal and postmenopausal women. Two published prospective studies reported a trend for a higher urinary 2-hydroxyoestrone:16 α -hydroxyoestrone ratio to be

associated with a reduced risk of breast cancer in premenopausal and postmenopausal women (Meilahn *et al.* 1998; Muti *et al.* 2000). However, studies that have investigated the effect of exercise and dietary interventions on this oestrogen metabolite ratio (to establish whether the pathway of oestrogen metabolism can be manipulated by lifestyle changes) have yielded inconsistent results (Longcope *et al.* 1987; Pasagian-Macaulay *et al.* 1996; Atkinson *et al.* 2004; Matthews *et al.* 2004; Campbell *et al.* 2005).

Of all the possible combinations of negative lifestyle interventions (low-fat diet with or without exercise, exercise alone), the most consistent evidence for an oestrogen-lowering effect exists for restricted dietary fat consumption. A number of mechanisms could explain the decrease in circulating oestrogen levels following reduced dietary fat consumption. Decreased rates of aromatisation in adipose tissue, leading to decreased oestradiol production, could result from a decrease in fat mass or through the conditions of negative energy balance modulating cellular enzyme activity (Heber *et al.* 1991). In addition, a reduction in dietary fat intake as part of an energy-restriction diet can affect β -glucuronidase activity in the intestinal flora (Goldin & Gorbach, 1976), which deconjugates biliary oestrogens so they can be reabsorbed from the intestinal tract, with the remaining conjugated oestrogens being excreted (Goldin *et al.* 1982). β -Glucuronidase activity increases with high-fat diets, especially high saturated fat intake (Goldin & Gorbach, 1976) which would decrease excretion. Increased faecal oestrogen excretion in vegetarian compared with omnivorous women may also support and emphasise an important role for dietary fibre in the control of oestrogen levels (Goldin *et al.* 1982). Added benefits of increasing fibre intake during the consumption of low-fat diets might accrue from the presence in high-fibre diets of naturally occurring substances with weak oestrogenic and anti-oestrogenic activity, which may induce production of SHBG in the liver and positively influence sex hormone metabolism and the resulting biological effects (Adlercreutz *et al.* 1986).

Insulin-like growth factor axis proteins and risk of hormone-related cancers

The IGF system consists of the IGF ligands (IGF-1 and IGF-2), cell surface receptors that mediate the biological effects of the IGF, including the IGF-1 and IGF-2 receptors, the insulin receptor and a family of IGF binding proteins (IGFBP-1–6) (LeRoith & Roberts, 2003). The IGF have an important role in normal growth and development, as well as in a variety of pathological situations, including tumorigenesis (Khandwala *et al.* 2000). IGF are potent mitogens for diverse cancer cell lines *in vitro* (Maloney *et al.* 2003) and also suppress apoptosis (Parrizas & LeRoith, 1997; Heron-Milhavet & LeRoith, 2002). Extensive evidence shows that breast cancer cells are responsive to exogenous IGF and tamoxifen reduces circulating IGF-1 levels (Pollak, 1998). IGF also exert strong mitogenic and anti-apoptotic effects on normal and transformed prostatic epithelial cells both *in vitro* and *in vivo* (Cohen *et al.* 1991; Angeloz-Nicoud & Binoux, 1995; Topping *et al.* 1997) and modulate growth of the prostate carcinoma cell lines LNCaP, PC-3 and DU-145 *in vitro* (Pietrkowski *et al.* 1993; Ngo *et al.* 2003). Up

Table 1. The effects of combined low-fat and aerobic exercise interventions on circulating levels of insulin, sex steroid hormones and/or insulin-like growth factor (IGF) axis proteins

Study	Subjects	Study design and intervention	Assessments	Main outcomes in relation to hormone-related cancers	Result
Pasagian-Macaulay <i>et al.</i> (1996)	Premenopausal women aged 44–50 years	Two-group randomised design: DE, low-fat (<25% total energy) diet and moderate-intensity walking exercise (<i>n</i> 84); C, assessment-only control group (<i>n</i> 90)	Baseline and after 6 months	Urinary oestrogen metabolites; 2-hydroxyoestrone:16 α -hydroxyoestrone ratio	DE \uparrow 9.6%; C \uparrow 12% (no difference in change between groups)
Tymchuk <i>et al.</i> (2000)	Postmenopausal women	Two-group cross-sectional comparison, (HRT (<i>n</i> 11) and non-HRT (<i>n</i> 11) groups): DE, residential ST low-fat (<10% total energy), high-fibre, complex-carbohydrate diet and daily aerobic exercise	Baseline and after 21 d	Body weight Serum insulin Serum SHBG	HRT \downarrow 4%; non-HRT \downarrow 3% HRT \downarrow 39%; non-HRT \downarrow 19% HRT \uparrow 39%; non-HRT \uparrow 42%
Barnard <i>et al.</i> (1992)	Men and women aged 21–78 years (mean age 57 years)	Three-group cross-sectional comparison for some measures (diabetic, insulin-resistant and normal controls): DE, residential ST low-fat (\leq 10% total energy), high-fibre diet (10–15% protein; 75–80% carbohydrate) and daily walking exercise for >30 min (<i>n</i> 72)	Baseline and after 26 d	Body weight Serum insulin	\downarrow 2 kg \downarrow 29%
Tymchuk <i>et al.</i> (1998)	Obese middle-aged men	Single-group design: DE, residential ST low-fat (<10% total energy), high-fibre diet (10–15% protein; 75–80% carbohydrate), daily 30–45 min walking and participation in supervised exercise class (<i>n</i> 27)	Baseline and after 21 d	Body weight Serum insulin Serum SHBG Serum PSA	\downarrow 5 kg \downarrow 43% \uparrow 39% No change
Tymchuk <i>et al.</i> (2002)	Middle-aged men	Two-group cross-sectional comparison: DE, LT low-fat (<10% total energy), high-fibre diet (10–15% protein; 75–80% carbohydrate) and daily aerobic exercise for 60 min (<i>n</i> 8); C, overweight controls on no special diet or exercise programme (<i>n</i> 14)	Outcome measures compared between groups at a single time point. Mean time on DE intervention was 14.2 years	Serum-stimulated LNCaP growth in cell culture v. FBS control DE v. C	DE \downarrow 40%; C slight \uparrow 49% lower in DE than C
Ngo <i>et al.</i> (2003)	Middle-aged men	Single-group design: DE, residential ST low-fat (\leq 10% total energy), high-fibre diet (10–15% protein; 75–80% carbohydrate) and daily aerobic exercise for 30–60 min (<i>n</i> 14)	Baseline and after 11 d	Serum-stimulated LNCaP growth in cell culture (v. baseline serum)	\downarrow 30% after 11 d

Ngo <i>et al.</i> (2002)	Obese middle-aged men	Two-group cross-sectional comparison: DE1, residential ST low-fat (<10% total energy), high-fibre diet (10–15% protein; 75–80% carbohydrate) and daily aerobic exercise for 60 min (<i>n</i> 14); DE2, LT low-fat (<10% total energy), high-fibre diet (10–15% protein; 75–80% carbohydrate) and daily aerobic exercise for 60 min (<i>n</i> 8)	Baseline and after 11 d in DE1. One sample taken in DE2 after an average time of 14.2 years on intervention and compared with baseline levels in DE1	<p>Body weight</p> <p>Serum insulin</p> <p>Serum IGF</p> <p>Serum IGFBP-1</p> <p>Serum IGFBP-3</p> <p>Serum-stimulated LNCaP growth in cell culture (<i>v.</i> baseline serum)</p> <p>Serum-stimulated LNCaP apoptosis in cell culture (<i>v.</i> baseline serum)</p>	<p>DE1 ↓ 4%; DE2 ↓ 38%</p> <p>DE1 ↓ 25%; DE2 ↓ 68%</p> <p>DE1 ↓ 20%; DE2 ↓ 55%</p> <p>DE1 ↑ 53%; DE2 ↑ 150%</p> <p>No change in DE1 or DE2</p> <p>DE1 ↓ 30%; DE2 ↓ 44%</p> <p>DE1 ↑ ;DE2 ↑ (larger ↑ in DE2 than DE1)</p>
Barnard <i>et al.</i> (2003)	Middle-aged sedentary men with poor dietary habits	Three-group cross-sectional comparison: DE, LT low-fat (<10% total energy), high-fibre diet (10–15% protein; 75–80% carbohydrate) and 4–6 d per week aerobic exercise (<i>n</i> 8); E, LT aerobic exercise 5 d per week (<i>n</i> 12); C, sedentary control group (<i>n</i> 14)	Outcome measures compared between groups at a single time point. Mean time on interventions was 14.2 years for DE and 10 years for E	<p>Serum insulin (% of controls)</p> <p>Serum IGF (% of controls)</p> <p>Serum IGFBP-1 (% of controls)</p> <p>Serum-stimulated LNCaP growth in cell culture (% of FBS control)</p> <p>Serum-stimulated LNCaP apoptosis in cell culture (% of FBS control)</p>	<p>DE 31%; E 40%</p> <p>DE 45%; E 41%</p> <p>DE 314%; E 191%</p> <p>DE 55%; E 65%; C 99%</p> <p>DE ↑ ; E ↑ ; C no difference (larger ↑ in DE than E)</p>
Rosenthal <i>et al.</i> (1985)	Middle-aged men with risk factors for CVD	Single-group design: DE, residential ST low-fat (<10% total energy), high-fibre diet (15–20% protein; 70–75% carbohydrate) and aerobic exercise for up to 60 min 4–6 d per week (<i>n</i> 21)	Baseline and after 26 d	<p>Body weight</p> <p>Serum oestradiol</p> <p>Serum testosterone</p> <p>Serum oestradiol:testosterone ratio</p>	<p>↓ 5%</p> <p>↓ 50%</p> <p>No change</p> <p>↓ 50%</p>
McTiernan <i>et al.</i> (1998a)	Sedentary overweight breast cancer patients aged 40–74 years (mostly post-menopausal)	Single-group pilot study (<i>n</i> 9): DE, moderate-intensity aerobic exercise on 6 d per week (three supervised sessions) and low-fat (20% total energy) diet	Baseline and at 8–10 weeks later	<p>Body weight</p> <p>Waist circumference</p> <p>% Body fat</p> <p>Total and free oestradiol</p> <p>Oestrone sulfate</p> <p>Total and free testosterone</p> <p>Androstenedione</p> <p>DHEA and DHEA-sulfate</p>	<p>1.2 kg reduction</p> <p>3.4 cm reduction</p> <p>2.3% reduction</p> <p>Slight decrease (NS)</p> <p>Slight decrease (NS)</p> <p>Slight decrease (NS)</p> <p>Slight decrease (NS)</p> <p>Slight decrease (NS)</p>

Table 1. Continued

Study	Subjects	Study design and intervention	Assessments	Main outcomes in relation to hormone-related cancers	Result
Ornish <i>et al.</i> (2005)	Patients with biopsy-documented prostate cancer who had elected not to undergo conventional treatment	Two-group randomised design: DE, low-fat (10% total energy) vegan diet and aerobic exercise 6 d per week; C, usual care control group	Baseline and at 1 year later	Body weight Serum PSA Serum-stimulated LNCaP growth in cell culture (% of FBS control) Serum-stimulated LNCaP apoptosis in cell culture (% of FBS control) Serum testosterone Serum CRP Patients needing conventional treatment due to ↑ PSA or disease progression	DE ↓ 4.5 kg; C no change DE ↓ 4%; C ↑ 6% DE 70%; C 9% No difference No change in DE or C Trend for greater ↓ in DE DE no patients; C six patients

DE, combined low-fat diet and aerobic exercise intervention; C, control group; ↑, increase; HRT, hormone replacement therapy; ST, short-term; ↓, decrease; SHBG, sex hormone-binding globulin; PSA, prostate-specific antigen; LT, long-term; LNCaP, androgen-dependent prostate cancer cell line; FBS, fetal bovine serum; IGF1BP, insulin-like growth factor binding protein; E, aerobic exercise-only intervention; DHEA, dehydroepiandrosterone; CRP, C-reactive protein.

regulation of IGF-1 receptor expression could augment the response to IGF-1. Compared with equivalent healthy tissues, the IGF-1 receptor is over-expressed in human malignancies, including cancers of the breast and prostate (Hellowell *et al.* 2002; Perks & Holly, 2003).

Hepatic production of IGF axis proteins is mainly dependent on growth hormone secretion (Janssen *et al.* 2004), but circulating levels are also affected by age and sex, insulin, nutritional status, the host response to systemic diseases such as cancer and endocrine therapy, whereas the locally expressed components are controlled by factors specific to each individual tissue (Rajaram *et al.* 1997; Perks & Holly, 2003). IGF-1 is the major bioactive component among the IGF and shares significant structural homology with insulin (Yu & Rohan, 2000). IGF-1 bioavailability is influenced by circulating free levels and production in the tissues, as well as tissue expression of the IGF receptors. However, IGF bioavailability in the circulation and extracellular fluids is also modulated by the IGFBP, which bind with varying relative affinity for IGF-1 and IGF-2 (Foulstone *et al.* 2005). The most frequently studied binding proteins in relation to cancer risk are IGFBP-1 and IGFBP-3, which are secreted primarily by the liver (Goodwin *et al.* 2002a). Over 90% of the circulating IGF-1 is bound in a ternary complex with IGFBP-3 (the most abundant circulating binding protein) and a glycoprotein, the acid-labile subunit, and this complex, which constitutes a storage pool of IGF-1 in the blood (Allen *et al.* 2003), is too large to cross the endothelial membrane. IGFBP-1 is a smaller protein structure that does not form a ternary complex and can pass to the extracellular tissue. Thus, IGFBP-1 is found predominantly in the tissues (although detectable levels circulate in the blood) and acts primarily to inhibit the physiological effects of IGF-1 (Rajaram *et al.* 1997). Changes in IGFBP production resulting from interventions or lifestyle changes affect IGF bioavailability. IGFBP are also subject to potentially regulating proteolysis by various proteases secreted by prostate and breast cancer cells that may act as growth stimulators by increasing local IGF bioavailability (Baxter, 2000).

A recent systematic review and meta-regression analysis of twenty-six datasets from twenty-one studies conducted by Renehan *et al.* (2004) showed that high circulating levels of IGF-1 (highest quartile *v.* lowest quartile) was associated with a 49% increased risk of prostate cancer and a 65% increased risk of premenopausal breast cancer, whereas no association was found for postmenopausal breast cancer. This comprehensive review considered evidence from fifteen prospective studies (usually nested within larger cohorts) and six case-control studies. Prospective studies are preferred because circulating levels of factors that could be implicated in cancer risk can be increased by the disease process itself, and this can undermine the predictive validity of case-control studies. However, re-analysis of the systematic review and meta-analysis presented by Renehan *et al.* (2004) showed that the strengths of association for prostate cancer and premenopausal breast cancer were increased when the case-control studies were omitted from the analysis (Holly, 2004).

No consistent association between higher circulating levels of IGFBP-3 and reduced risk of hormone-related cancers was found in a recent systematic review and meta-analysis (Renehan *et al.* 2004) and the association between circulating IGFBP-1 and cancer risk has been less well studied. In postmenopausal breast cancer patients, circulating levels of IGFBP-1 significantly predicted distant disease recurrence and death (but the effects were not independent of fasting insulin levels), whereas circulating IGFBP-3 concentrations only predicted distant disease recurrence (Goodwin *et al.* 2002a). However, no association between circulating IGFBP-3 and disease recurrence or disease-free survival was reported in another study (Rocha *et al.* 1997). In prostate cancer patients, serum IGFBP-3 levels were low in comparison with normal controls (Kanety *et al.* 1993) and lower in patients with advanced disease *v.* those with localised tumours and benign prostate hyperplasia (Miyata *et al.* 2003). There is evidence that IGFBP-1 and IGFBP-3 can inhibit the growth of breast and prostate cancer cell lines *in vitro* (Figuroa *et al.* 1995; Butt *et al.* 2002; Wilson *et al.* 2002). As IGFBP limit IGF bioavailability, increased circulating and/or tissue levels could blunt the proliferative effect of IGF on normal and transformed cancer cells. In addition, binding protein proteases such as PSA can modulate IGF bioavailability in the cellular milieu (Pollak, 1998). In this respect, the IGFBP-3:PSA ratio was identified as an independent predictor of relapse-free and cause-specific survival in advanced prostate cancer patients who were treated with hormonal therapy (Miyata *et al.* 2003). However, in some cellular environments IGFBP-3 is anti-apoptotic, as shown with the Hs578T breast cancer cell line (McCaig *et al.* 2002) and this might explain the recently reported positive association between higher IGFBP-3 and premenopausal breast cancer risk in a recent systematic review and meta-analysis (Renehan *et al.* 2004).

Dietary energy restriction, physical activity and circulating insulin-like growth factor axis proteins

IGF-1 levels decrease in response to fasting and protein-energy malnutrition, but levels are restored in response to improvements in energy intake and are increased above normal levels and overfeeding (Yu & Rohan, 2000). IGFBP-1 levels are also influenced by nutritional state, with serum levels being highest during fasting and lowest in the fed state, and an inverse association between circulating IGFBP-1 concentration and insulin secretion (Musey *et al.* 1993; Ferry *et al.* 1999). A 50% reduction in energy intake over 6 d caused a significant increase in IGFBP-1 in normal adults (Smith *et al.* 1995). Conversely, circulating IGFBP-1 levels are chronically reduced in conditions of elevated fasting insulin levels, such as obesity and insulin resistance (Kaaks & Lukanova, 2001). Although circulating IGFBP-3 may be less acutely affected by the metabolic state (Underwood *et al.* 1994; Smith *et al.* 1995), circulating IGFBP-3 decreases with prolonged energy and/or protein restriction (Smith *et al.* 1995; Underwood, 1996).

Short-term vigorous aerobic exercise training (in the absence of frank over-feeding) appears to decrease the circulating IGF-1, even in weight-stable individuals

(Nemet *et al.* 2004). However, evidence for an attenuating effect of regular moderate intensity physical activity on circulating IGF-1 levels is equivocal, as the association between a physically active lifestyle and circulating IGF-1 axis proteins is complex (for a review, see Yu & Rohan, 2000), being confounded by dietary patterns, age and type of physical activity performed. In premenopausal women, a non-significant trend for increased levels of physical activity to be associated with lower IGF-1 and IGFBP-3 levels and increased levels of IGFBP-1 was reported by Voskuil *et al.* (2001), whereas a 12-month moderate-intensity aerobic exercise programme (5 d/week) had no effect on serum concentrations of IGF-1 or IGFBP-3 (or the ratio of the two) in overweight postmenopausal women (McTiernan *et al.* 2005). Furthermore, there were no changes in resting circulating levels of IGF-1, IGFBP or testosterone following a 6-month programme of resistance training in women aged 60–85 years (Borst *et al.* 2002) or following a 12-week programme of endurance exercise in elderly women (Lange *et al.* 2001). Similar findings have been reported following a strength training programme in postmenopausal breast cancer survivors (Schmitz *et al.* 2005a). However, significantly greater changes in circulating levels of IGF-1 (decrease), IGFBP-3 (increase) and the IGF-1:IGFBP-3 ratio (decrease) were observed following a 15-week aerobic exercise intervention in women recovering from breast cancer treatment *v.* a patient control group (Fairey *et al.* 2003). In this study, there was no difference between the increases in circulating IGFBP-1 recorded for the exercise (+5.6%) or control (+4.2%) groups and weight loss was minimal, showing that potentially beneficial changes in IGF axis proteins can be induced by exercise without loss of body weight (Fairey *et al.* 2003). The authors also highlighted the similarity of changes in IGF axis proteins evoked by oestrogen receptor modulation therapies (raloxifene and tamoxifen) in postmenopausal breast cancer survivors. The strengths of the latter two studies include the randomised controlled designs, high exercise adherence rate, and with minimal loss to follow-up, although subject numbers were limited to between twenty-five and thirty-six in the exercise and control groups.

In middle-aged men, a series of insightful studies have investigated the effects of exercise, low-fat diets and combined low-fat diet and exercise programmes on IGF axis markers and the mechanisms by which these interventions might help to reduce the risk of prostate cancer. The effects of short- and long-term combined programmes of low-fat diet and aerobic exercise on circulating IGF axis proteins and insulin were compared in overweight middle-aged men by Ngo *et al.* (2002). Men recruited for the short-term programme consumed a low-fat diet (<10% fat, 10–15% protein and 75–80% carbohydrate) and participated in daily aerobic exercise (60 min/d) for 11 d. These were compared with men who had been following a similar regimen for an average of 14.2 years. The researchers also examined the effects of changes in circulating IGF axis proteins and sex steroid hormones on prostate cancer cell growth *in vitro* by incubating baseline and post-intervention serum with the androgen-dependent prostate cancer cell line LNCaP in cell culture. Fasting insulin levels were 25 and 68% lower than baseline levels following the short- and long-term combined

programmes, respectively, corresponding to decreases in serum IGF-1 of 20 and 55%, increases in IGFBP-1 of 53 and 150% and decreases in body weight of 4 and 38%, respectively. There was no change in circulating IGFBP-3 concentration in either group. LNCaP apoptosis was increased and cell growth inhibited by 30% (short-term intervention) and 44% (long-term intervention) when cells were incubated with post-intervention serum *v.* baseline serum in the cell-culture experiments. Serum levels of IGF-1 and IGFBP-1 were positively and negatively correlated with LNCaP growth, respectively (Table 1).

In another study by the same group, similar positive changes in fasting insulin and IGF axis proteins to those observed following the long-term combined diet and exercise programme were apparent in men who had been engaged in a long-term exercise intervention for an average time of 10 years (Barnard *et al.* 2003). However, the increase in circulating IGFBP-1 was reported to be greater in men who had been following the long-term combined programme than in men engaged in long-term exercise only. LNCaP cell growth was inhibited to a similar degree when incubated with serum from men on the two interventions in relation to control serum in cell culture, but significantly greater apoptosis was observed when LNCaP cells were incubated in serum from men on the combined diet and exercise intervention. This later finding could have been influenced by the greater change in IGFBP-1 observed in the group following the combined programme as all other changes in serum factors were similar (Table 1).

Other studies by the same group showed that even though the long-term combination of low-fat diet and regular exercise reduced circulating levels of sex hormones in the middle-aged men (Rosenthal *et al.* 1985), changes in IGF axis proteins were shown to be mainly responsible for the ability of post-intervention serum to inhibit prostate cancer cell growth in the cell-culture experiments. Adding sex steroid hormones and insulin back to the diet and exercise serum, so that levels were comparable with baseline measures before incubation with the LNCaP cells, showed that reductions in serum oestradiol, free testosterone and insulin induced by the diet and exercise intervention accounted for only half of the inhibitory effects on cell growth observed (Tymchuk *et al.* 2002). However, the inhibition of LNCaP cell growth was completely eliminated by adding back IGF-1 (Barnard *et al.* 2003). Furthermore, when IGFBP-1 was added to baseline serum, LNCaP growth was reduced and apoptosis induced (Ngo *et al.* 2003). This series of studies has yielded some very interesting data on the effects of low-fat dietary and moderate-intensity exercise interventions on IGF axis proteins and sex steroid hormones, and the mechanisms by which such changes could influence prostate cancer development. However, small subject numbers, cross-sectional designs or the lack of a control group and the problem of extrapolating *in vitro* cell-culture data to the *in vivo* situation are significant limitations.

In a more recent randomised controlled trial in men with early biopsy-proven prostate cancer who had chosen not to undergo any conventional treatment (thus controlling for the confounding effects of treatment interventions), the effects of a 1-year very-low-fat vegan diet and moderate intensity exercise intervention on PSA, treatment trends and

serum-stimulated LNCaP growth were investigated (Ornish *et al.* 2005). After 1 year, PSA had increased by 6% in the controls and decreased by 4% in the intervention group. Body weight decreased by 4.5 kg in the intervention group and was unchanged in the controls. Six of the forty-nine control patients went on to conventional treatment (due to rising PSA) compared with none of the forty-four patients in the intervention group. In the serum-stimulated LNCaP assay, cell growth was reduced by 9% in the controls and by 70% in the intervention group, but there was no difference between the groups in apoptosis or serum testosterone concentration. The intention is to follow the patients for a longer time period to establish the effect of the intervention on disease recurrence rates and mortality.

Negative energy balance interventions and insulin resistance

Exercise with or without dietary interventions that promote negative energy balance has the potential to improve insulin resistance, which could profoundly influence any beneficial changes in circulating sex steroid hormones and/or IGF axis proteins with respect to cancer risk. Insulin stimulates the hepatic production of IGF and their growth-promoting effects and inhibits IGFBP-1 production (Thissen *et al.* 1994; Yu & Rohan, 2000). By inhibiting IGFBP production, insulin may further increase IGF-1 bioavailability. The regulatory effect of insulin and IGF-1 on SHBG production and sex hormone bioavailability could also have important implications for the development of hormone-related cancers. Insulin and IGF-1 suppress hepatic production of SHBG, resulting in more free testosterone and oestradiol to stimulate cell growth (Plymate *et al.* 1988; Singh *et al.* 1990; Pasquali *et al.* 1995). Insulin is also a potent mitogen for various cell lines, mediating glucose transport across the cell membrane to provide an energy source and directly activating cellular RNA and protein production via the mitogen-activating protein kinase pathway (King & Kahn, 1981). Insulin has been shown to induce mitogenic effects on normal and malignant breast epithelial cells (Belfiore *et al.* 1996; Papa & Belfiore, 1996) and prostate cancer cells (Polychronakos *et al.* 1991) *in vitro* and elevated circulating insulin is reported to be a risk factor for breast cancer (Bruning *et al.* 1992; Hirose *et al.* 2003) and prostate cancer (Hsing *et al.* 2001, 2003). In addition, high fasting insulin levels have been associated with distant recurrence and death in breast cancer survivors (Goodwin *et al.* 2002b) and visceral fat area and high visceral fat:subcutaneous fat ratio (as quantified by computer tomography) was shown to be associated with a greater than four-fold increased risk of prostate cancer (von Hafe *et al.* 2004).

Lower BMI, higher levels of physical activity and lower energy intake were all independently associated with lower fasting insulin levels in a recent large-scale study of mostly healthy postmenopausal women (Chlebowski *et al.* 2004). Dietary-induced weight loss improves insulin sensitivity in obese men (Ross *et al.* 2000). However, regular exercise without dietary energy restriction has also been shown to improve insulin sensitivity (Ross *et al.* 2000, 2004). Improvements in insulin sensitivity following negative energy balance interventions may be mediated by weight

loss (Niskanen *et al.* 1996; Goodpaster *et al.* 1999), although improved insulin sensitivity has not been accompanied by weight loss in all exercise intervention studies (Duncan *et al.* 2003). Furthermore, changes in fasting serum insulin levels have been observed after only 2–3 weeks of diet and exercise interventions, even though the individuals remained obese (BMI > 30 kg/m²) (Barnard *et al.* 1992; Tymchuk *et al.* 1998; Ngo *et al.* 2002).

Exercise-induced effects on insulin sensitivity that are attributable to weight loss might be associated with the effects of negative energy balance on visceral fat stores. Evidence suggests that weight loss from energy restriction alone causes diffuse fat and lean tissue mass reductions, sometimes with minimal effects on visceral fat (Wood, 1993) which is the most metabolically active fat depot (Krotkiewski *et al.* 1983). However, aerobic exercise preferentially causes reduction in visceral fat in men (Schwartz *et al.* 1991) and women (McTiernan *et al.* 1998b) and a 1–2 kg reduction in visceral fat can have profound effects on glucose tolerance, fasting insulin and blood lipid levels (Krotkiewski *et al.* 1983). In postmenopausal women and middle-aged men, interventions comprising low-fat, high-carbohydrate diets in conjunction with moderate-intensity exercise training that resulted in a decrease in fasting insulin concentration, were accompanied by an increase in circulating SHBG (Tymchuk *et al.* 1998, 2000). However, in postmenopausal breast cancer survivors, positive changes in circulating IGF axis proteins (including IGF-1 and IGFBP-3) after 15 weeks of moderate-intensity aerobic exercise training were independent of changes in fasting insulin or insulin resistance (Fairley *et al.* 2003).

Other potential benefits of negative energy balance interventions in cancer survivors

Continued advances in early-detection and effective treatments have resulted in the hope of longer survival and even cure for many cancer patients. Despite an increase in UK cancer incidence in the 10-year period between 1994 and 2003, overall mortality from cancer decreased (Cancer Research UK, 2005b). Furthermore, survival data for cancer diagnosis during the period 1996–9 in the UK (Cancer Research UK, 2005c) showed that both breast and prostate cancer fell into the highest 5-year survival category (77% for breast cancer; 65% for prostate cancer). With the increasing ageing population, the number of elderly cancer survivors is expected to double over the next 50 years (Demark-Wahnefried *et al.* 2004), which means that disease recurrence and the risk of secondary primary cancers is becoming an important issue in the management of cancer patients.

Given the increase in life expectancy following a cancer diagnosis, promotion of healthy lifestyle behaviours among survivors might help them to enjoy a higher level of physical functioning, improved cardiovascular health and better health-related quality of life. Older individuals diagnosed with cancer are at increased risk of other cancers and chronic age-related conditions and are susceptible to functional losses that can threaten independent living (Aziz, 2002; Hewitt *et al.* 2003). It has been argued that physical activity, diet and/or weight-control interventions hold considerable promise for ameliorating the adverse

sequelae of cancer (Aziz, 2002). Studies have shown that participation in regular physical activity and the consumption of healthy low-fat diets during and/or after treatment are associated with higher levels of physical functioning, reduced feelings of fatigue and improved health-related quality of life among breast and prostate cancer survivors (Demark-Wahnefried *et al.* 2004; Knols *et al.* 2005; Schmitz *et al.* 2005b). Nevertheless, the specific beneficial effects of exercise may vary as a function of disease stage, treatment approach and current lifestyle of the patient (Knols *et al.* 2005) and the full range of positive effects resulting from physical activity is as yet unknown (Schmitz *et al.* 2005b). In addition, the methodological quality of most studies has been moderate, highlighting the need for more robustly designed randomised controlled trials with larger populations of cancer survivors (Aziz, 2002; Knols *et al.* 2005).

The beneficial effects of physical activity might also extend to anti-tumour defences in cancer patients, which could reduce the risk of disease recurrence and second cancers (Aziz, 2002). Chemotherapy following a cancer diagnosis suppresses immune function, including a reduction in circulating T-helper (CD4⁺) cells and an impairment of natural killer (NK) cell function (Head *et al.* 1993; Sewell *et al.* 1993; Hakim *et al.* 1997). In addition to the effects of treatment *per se*, the physiological effects of stress associated with a cancer diagnosis might further inhibit cellular immune responses that are relevant to cancer prognosis, including NK cell toxicity and T-cell responses (Andersen *et al.* 1998). The adverse effect of psychosocial stressors on immune function is considered to be mediated by excess secretion of the stress hormone cortisol and the catecholamines (McEwen & Stellar, 1993; Madden & Felten, 1995). Elevated cortisol and catecholamine levels evoked by psychological stressors can significantly influence immune function, including lymphocyte proliferation and NK cell activity (Banu *et al.* 1988; Benschop *et al.* 1994; Bryla, 1996; Kronfol *et al.* 1997). Self-reported negative mood states have been associated with lower NK cell activity (Levy & Herberman, 1985; Levy *et al.* 1991) and symptoms of depression have been linked with increased salivary cortisol (Ehlert *et al.* 1990), impaired lymphocyte proliferation (Schleifer *et al.* 1984; Maes, 1995) and reduced NK cell cytotoxicity against tumour cells (Neruzzi *et al.* 1989; Caldwell *et al.* 1991; Maes *et al.* 1992). Studies have reported abnormal circadian rhythmicity of cortisol in breast cancer patients (Touitou *et al.* 1996; van der Pompe *et al.* 1996; Sephton *et al.* 2000; Abercrombie *et al.* 2004) and flattened or abnormal diurnal salivary cortisol rhythms have recently been associated with earlier mortality in breast cancer patients (Sephton *et al.* 2000) and persistent fatigue in survivors 1–5 years after initial diagnosis (Bower *et al.* 2005).

Regular physical activity can have a positive effect on psychological health status and quality of life in cancer survivors (Baldwin & Courneya, 1997; Courneya & Friedenreich, 1997) that could enhance immune function through normalisation of stress hormone levels. Alternatively, changes in circulating sex hormone levels might influence the functioning of immune cells in peripheral blood. Sex hormones have been reported to exert immunoregulatory effects both *in vivo* and *in vitro* (Paavonen, 1994), with

evidence of suppressive effects for progesterone and the androgens, whereas oestrogens can be suppressive or stimulatory depending on the situation (van Vollenhoven & McGuire, 1994). Peters *et al.* (1994; 1995) reported an increase in the percentage of NK cells and an improvement in NK cell function and monocyte phagocytic capacity in breast cancer survivors that was accompanied by an increase in 'satisfaction of life' score after 7 months of moderate exercise training. Two recent studies have consolidated this finding with reports of improved immune function in postmenopausal women treated for breast cancer following a period of aerobic exercise or combined aerobic exercise and resistance training lasting for 4–6 months (Fairey *et al.* 2005; Hutnick *et al.* 2005). An increase in T-helper cell activation was observed in patients randomised to an exercise group after receiving chemotherapy in comparison with control non-exercising patients who had received chemotherapy (Hutnick *et al.* 2005). In the other study, an improvement in NK cell cytotoxic activity and in unstimulated lymphocyte proliferation was observed in breast cancer patients randomised to aerobic exercise training following surgery, radiotherapy and/or chemotherapy with or without hormone therapy, in comparison with non-exercising control patients (Fairey *et al.* 2005). Although the underlying mechanisms for exercise-induced improvements in immune function are poorly understood, further studies are warranted, as lifestyle interventions which could have an impact on anti-tumour defences could have a significant influence on disease-free survival in cancer survivors.

Summary and conclusions

Obesity, physical activity status and circulating levels of sex steroid hormones and IGF axis proteins are intrinsically linked to energy balance. Epidemiological studies have reported a positive association between obesity and breast cancer risk for postmenopausal women, but with the role of central adiposity being more equivocal. However, recent evidence suggests that increased central adiposity is strongly associated with the risk of prostate cancer. In addition, obesity is associated with poorer prognosis following a breast or prostate cancer diagnosis. Evidence for a protective effect of increased physical activity levels on hormone-related cancer risk appears to be stronger for breast cancer than prostate cancer at the present time, with recent data also showing that physically active breast cancer survivors have an improved chance of longer-term survival. The link between physical activity status and disease-free survival has not yet been studied in prostate cancer patients, although one study (Ornish *et al.* 2005) reported positive results in prostate cancer patients undergoing a combined exercise and low-fat diet intervention. A stronger association between circulating oestrogen levels and breast cancer risk has been reported for postmenopausal than premenopausal women and is linked to an increased aromatase activity in heavier postmenopausal women. Higher circulating testosterone is associated with an increased risk of prostate cancer and the role of oestrogen metabolism in the development of this disease warrants further study. Higher circulating IGF-1 is also associated with an increased risk of developing prostate

cancer and breast cancer in premenopausal but not postmenopausal women, whereas a high circulating level of IGFBP-3 is associated with an elevated risk of premenopausal breast cancer.

An increasing number of intervention studies in 'at-risk' individuals and in patients recovering from cancer treatment are now investigating the effects of lifestyle interventions that promote negative energy balance on circulating levels of sex hormones and IGF axis proteins as surrogate markers of cancer risk. In relation to such lifestyle interventions, the most consistent evidence for a sex steroid hormone-lowering effect exists for oestrogen following restricted dietary fat consumption with or without regular exercise. For circulating proteins of the IGF-axis, evidence derived predominantly from middle-aged 'at-risk' men suggests that combining very-low-fat diets ($\leq 10\%$ of total energy) with regular physical activity can induce significant changes in IGF-1 and IGFBP-1 that could protect against the development or progression of prostate cancer. One recent randomised controlled trial also reported positive results in breast cancer survivors (Fairey *et al.* 2003). Recent evidence also suggests that lifestyle interventions associated with negative energy balance can lead to improvements in physical function and reduced feelings of fatigue, improved anti-tumour defences and an enhancement of health-related quality of life in cancer survivors. Nevertheless, the methodological quality of most intervention studies has been limited due to small subject numbers, lack of adequate control groups or non-randomised designs and a number of significant questions remain. For example, it is not known which combination of specific dietary and physical activity interventions work best for reducing the risk of hormone-related cancers in younger and older obese and non-obese populations, nor whether it is possible to get similar protective effects from dietary energy restriction and physical activity alone in these populations. Second, the optimal dose–response relationship for reducing cancer risk by dietary energy restriction and/or physical activity interventions in these different groups is unknown. Most intervention studies investigating the combined effect of diet and exercise have involved the consumption of very-low-fat-diets ($\leq 10\%$ of total energy) and the effect of less intensive reductions of dietary fat and energy intake, with and without simultaneous exercise participation is currently unknown. Third, more studies investigating the association between lifestyle interventions that promote negative energy balance and disease recurrence and/or secondary primary tumours in cancer survivors are needed following promising results from very recent trials. Fourth, the predictive validity of some of the circulating biomarkers being used to assess the risk of hormone-related cancers requires further investigation. Improved knowledge about the degree to which changes in a given surrogate end-point reflects changes in clinically meaningful end-points, such as cancer diagnosis or disease-free survival, is urgently needed. More intervention studies with randomised controlled designs, higher subject numbers and longer-term follow-up measures in 'at-risk' populations and survivors are necessary to answer these questions and to establish the magnitude of change required in surrogate markers to induce a protective effect.

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