Lifestyle and Exercise after Cancer

An Evidence Review for the Self-Management Work stream of the National Cancer Survivorship Initiative

Professor Robert Thomas
Nicola Davies
Lynn Bateup

Authors

Robert Thomas FRCP MD FRCR
Visiting Professor Cranfield University
Consultant Oncologist
Bedford Hospital & Addenbrooke's Hospital Cambridge University NHS Trusts,
c/o The Primrose Unit, Bedford Hospital, Bedford MK42 9DJ.
Rt@cancernet.co.uk

Nicola Davies BSc (Hons); MSc Comm.; PhD Researcher
Evaluation and Research Coordinator, Self-Management Workstream,
National Cancer Survivorship Initiative,
Macmillan Cancer Support;
NDavies@macmillan.org.uk.

Lynn Bateup
Project Manager, Self-Management Workstream,
National Cancer Survivorship Initiative,
Macmillan Cancer Support;
Lbatehup@macmillan.org.uk.

CONTENTS

Introduction

It has been firmly established in scientific literature that regular exercise and a healthy lifestyle reduces the risks of developing cancer. In fact, The World Cancer Research Fund estimate that over 80,000 patients diagnosed with cancer each year could have avoided the disease by adopting a healthier lifestyle. This amounts to 39% of cases of the twelve major cancers which could be prevented through better diet, drinking, and exercise habits.

What has been previously less well known is the evidence that exercise and a healthy lifestyle can also benefit individuals after a diagnosis of cancer, not only in terms of improved physical and psychological well-being, but also disease outcomes. This report, commissioned as part of the Supportive Self-Management Workstream of the National Cancer Survivorship Initiative (NCSI), seeks to review the lifestyle evidence and key findings pertaining to cancer and survivorship in order to provide more specific and tailored lifestyle recommendations. Hopefully, this evidence can help convince and reassure patients and their family that the extra efforts required to change a lifestyle, especially after the trauma of cancer and its treatment, are worthwhile. Furthermore, it may help convince healthcare commissioners to incorporate and fund self-management lifestyle initiatives into routine clinical practice. Finally, it may help academic bodies to design and fund clinical trials in areas where further evaluation is needed.

This report summarises the evidence that diet, exercise and other lifestyle factors can have on two fundamental issues after cancer:

Part One - The influence on cancer outcomes

- The rate of progression of an established prostate cancer
- The incidence of relapse
- The overall survival

Part Two - The influence on risks, side-effects and improved well-being;

- Cancer related fatigue
- Body constitution
- Psychological well-being
- Quality of life
- Lymphoedema
- Bone health

The data was obtained from a systematic search of the Cochrane Database of Systematic Reviews (CDSR), MEDLINE, and Google Scholar as well as from papers collected by the Primrose Oncology Research team for a series of review articles (Thomas et al., 2009; Davies et al., 2008), background evidence for the design of a double blind RCT (Thomas et al., 2007), and development of patient lifestyle information strategies including self-help manuals and books (Thomas et al., 2009; Health Education Publications, 2008). This review aimed to

highlight the best published examples, for each section, from available large cohort, prospective or randomised studies.

PART ONE

Evidence that Lifestyle can Influence Cancer Outcomes

Cancer Progression,

Relapse, and

Overall Survival

LIFESTYLE'S INFLUENCE ON CANCER PROGRESSION

A link between adopting a healthy lifestyle and a reduction in the rate of established cancer progression is now emerging in the published literature. So far it only involves men with indolent or relapsing prostate, where slow progression allows time for alternative interventions (Thomas et al., 2006). The underlying mechanisms for the direct anti-cancer effect of lifestyle, in this setting, has been suggested in a study which took serum from men undergoing a low-fat, high-fibre diet and exercise intervention programme and added it to androgen-dependent LNCaP cells in the laboratory. There was decreased growth and increased apoptosis, associated with a reduction in serum IGF-I. When IGF-I was added back to the post-intervention samples, this effect was lost. The p53 protein content was also found to be increased and NFkB activation reduced in the post serum-stimulated LNCaP cells. Similar results were observed when the IGF-I receptor was blocked in the pre-intervention serum (Soliman et al., 2009).

A number of epidemiological and cohort studies, have demonstrated that individuals with healthier lifestyles tend to present with less aggressive cancers, so their prognosis is better (Chan et al., 2005; Sonn, Aronson, and Litwin, 2005; Wilkinson and Chodak, 2003). For example, the health professionals study showed that men who consumed tomatoes, tomato sources, and olive oil developed prostate cancers which were less likely to have spread beyond the gland (Giovannucci et al., 2002). A large case-control study conducted in China demonstrated significantly lower grades of prostate cancer among individuals who regularly consumed foods containing tofu, soy and isoflavones (genistein and daidzein) compared to a matched cohort (Lee et al., 2003).

Although diets with good soya and tomato intake appear to be beneficial, taking additional soya or lycopene supplements appears not to be. A phase II study evaluated the effects of a low-fat diet or a low-fat diet with the addition of a soy supplement in asymptomatic, hormonally naive prostate cancer patients with rising prostate-specific antigen (PSA) levels. Patients were commenced on a low-fat diet with a goal to reduce fat intake to 15% of total daily calories. Serum was analysed for changes in the sex hormone and insulin-like growth factor (IGF-I) axes. Among 18 evaluable patients (median follow-up of study 10.5-months), there was a significant trend toward a longer PSA doubling time and a prolongation in estimated median TTP of 3-months. After the intervention, free testosterone levels significantly decreased by 5%. On PSA progression, a soy protein supplement was added to the diet, however, this did not reduce PSA levels or prolong the doubling time and IGF-I levels actually increased by 22%, risking a potentially undesirable biochemical effect (Spentzos et al., 2003).

Kucuk et al. (2002) reported a small prospective clinic study in men with localised prostate cancer (n = 26) awaiting prostatectomy, where the biological and clinical effects of lycopene

supplementation were investigated. The men were randomly assigned to receive oleoresin, a tomato extract, containing 30mg of lycopene (n = 15) or no supplementation (n = 11) for 3-weeks before radical prostatectomy. Biomarkers of cell proliferation and apoptosis were assessed in benign and cancerous prostate tissues. After the intervention, subjects in the intervention group had smaller tumours (80% vs 45%, less than 4ml), less involvement of surgical margins and/or extra-prostatic tissues with cancer (73% vs 18%, organ-confined disease), and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia (33% vs 0%, focal involvement) compared with subjects in the control group. Mean plasma PSA levels were lower in the intervention group compared with the control group. This pilot study suggested that lycopene may have beneficial effects in established prostate cancer.

Schwarz et al. (2008) report a second randomised study, not involving men with cancer, which demonstrated an effect on PSA in men with benign prostatic hyperplasia (BPH) who are at an increased risk of progressing to cancer. This pilot study randomly compared the effects of lycopene (15mg od) supplementation in elderly men (n = 20) diagnosed with BPH against those who were given placebo (n = 20), both taken for 6-months. The lycopene supplementation significantly decreased PSA levels, whereas there was no change in the placebo group. The plasma lycopene concentration increased in the group taking lycopene, but other plasma carotenoids were not affected. Whereas progression of prostate enlargement occurred in the placebo group as assessed by trans-rectal ultrasound and digital rectal examination, the prostate did not enlarge in the lycopene group. Symptoms of the disease, as assessed via the International Prostate Symptom Score questionnaire, were improved in both groups with a significantly greater effect in men taking lycopene supplements

Since these two studies offer a small sample size and short intervention period, further analysis in a much larger clinical study needs to be performed before lycopene supplements can be recommended.

McLarty et al. (2009) from Louisiana State University have found that green tea may reduce the levels of some compounds linked to prostate cancer progression. Through their study of prostate patients (n = 26) who were given a concentrated extract of tea polyphenols for an average of 34-days, they report a significant reduction in the levels of several growth factors that promote cancer as well as reductions in PSA. Furthermore, some men had reductions in growth factors of up to 30%. However, according to a newspaper report, *"the response varied among the men for reasons that researchers don't yet understand."*

Three prospective clinical studies seem to support the benefits of a healthy lifestyle as opposed to dietary supplements (Ornish et al., 2005; Thomas et al., 2005; Pantuck et al., 2006).

Ornish et al. (2005) published a randomised study of 93 volunteers with early prostate cancer from the USA, who had opted not to undergo conventional therapies. They were randomly assigned to intensive nutritional counselling and lifestyle changes, or not, as part of their

active surveillance. The lifestyle changes in this study included a vegan diet supplemented with soy, vitamin E, fish oils, selenium, and vitamin C, together with a moderate exercise program and stress management techniques such as yoga. PSA levels decreased by 4% at 12-months in the intervention group, but increased by 6% in the control group; this was statistically significant. As a secondary end point, serum taken from patients from the intervention group and introduced to prostate cell lines in vitro were eight times more likely to inhibit their growth than the control arm (70% v 6%). Furthermore, changes in PSA and cell line growth strongly correlated with the degree of lifestyle change.

Pantuck et al. (2006) published a prospective phase two study evaluating men with PSA relapse post-radiotherapy or prostatectomy (n = 48), comparing PSA doubling time (PSAdt) before and after the consumption of approximately 200ml pomegranate juice. There was a significant prolongation of PSAdt from a mean of 15-months at baseline to 54-months post-treatment. As a secondary end point, the patients' baseline oxidative state was significantly lower at baseline and after pomegranate consumption, measured using three separate serum analyses (serum induced proliferation and apoptosis of LNCaP cells, serum lipid peroxidation and serum nitric oxide levels).

A third, NCRN registered study, focused on lifestyle in combination with dietary supplements and salicylates in an attempt to inhibit the Cyclooxidase-2 (COX-2) pathway. COX-2 is over-expressed in approximately 75% of malignancies (Madaan et al., 2000) and humans. Several retrospective and prospective analyses have found an association with use of salicylates and lower incidence of prostate, bowel and breast cancers (Baron et al., 2003; Harris, Namboodiri, and Rusk, 1996; Sandler et al., 200; Thomas et al., 2005).

Thomas et al. (2007) designed and published a double blind trial involving men with progressive prostate cancer (n = 110), defined by three consecutive rises in PSA. All men received monthly counselling on healthy lifestyle and were randomised to salicylate alone or salicylate plus dietary supplements (Vitamin C, copper and manganese gluconate). The analysis at twelve-months showed no additional benefit from the supplements but nearly 40% of the entire group demonstrated a significant slowing or halting of PSA progression.

Conclusion and Recommendations: Although these trials are relatively small, they suggest a useful role for dietary and exercise advice for men with prostate cancer as a complement to active surveillance. Laboratory data suggest that soy supplements may be potentially harmful and lycopene has no effect, contradicting a small clinical study. Clearly further studies are required before dietary supplements can be considered in men with prostate cancer on active surveillance.

LIFESTYLE'S INFLUENCE ON RELAPSE RATES AND SURVIVAL

Influence of Diet

The association between dietary factors and survival from breast cancer has been derived from follow-up and case-control studies (Holmes et al., 1999; Rohan, Hiller, and McMichael, 1993). The largest of these is the Nurse's Health Study in which women with breast cancer completed a dietary questionnaire one-year following radical therapy. Women following their description of a *prudent* diet (high fruit, vegetable and fiber; low fat and salt) had a statistically significant lower overall mortality rate compared to those with a typical western diet. The specific breast cancer mortality overall was not, however, different except in the comparison of the upper quartile of prudent with the upper quartile of western and then only in a node positive subgroup (Kroenke et al., 2005).

For patients with colon cancer, a study published in JAMA in 2007 looked at dietary patterns in 1009 patients who had been successfully treated for stage III disease using a questionnaire at 6-months. Patients were then followed up for a median of 5.3-years, during which time there had been 324 relapses and 223 cancer related deaths. The questionnaire characterised dietary patterns into *Prudent* (high intake of fruit, vegetable, poultry, fish) and *Western* (high intake of meat, fat, refined grains, sweets and desserts). Comparing patients in the upper and lower quartile of a western pattern, there was a significant difference in disease free survival, recurrence free survival and overall survival (Meyerhardt et al., 2007).

The Women's Healthy Eating and Living Trial study from California evaluated the benefit of prospective dietary advice in 2,967 breast cancer survivors. They were randomly assigned to receive a five-a-day dietary guideline or to enter a control group. The intervention, significantly improved vegetable/fruit servings, fibre and fat intake compared to controls. Adjusting for tumour characteristics and hormonal treatment, women who did not experience hot flushes had 31% fewer events than similar women assigned to the comparison group (hazard ratio [HR] = 0.69; 95% CI, 0.51 to 0.93; P = .02). But interestingly, the intervention did not significantly affect prognosis in the women who reported regular hot flushes. This effect was thought to be caused by the fact that women with hot flushes ate better in both groups and irrespective of the intervention had a better outcome than those without hot flushes (Gold et al., 2009).

Similar results were found by Pierce et al. (2007), who examined a combination of diet and exercise among 1490 women who had been treated for breast cancer. Women who ate five or more servings of fruit and vegetables a day and were physically active for at least 30-minutes 6-days a week had a higher 10-year survival (Pierce et al., 2007).

The most robust data has been derived from a prospective trial which randomised 2,437 post-menopausal women with early breast cancer to receive nutritional and lifestyle counselling, or

not, as part of routine follow-up. The dietary intervention included eight bi-weekly individual counselling sessions. Dietary fat intake reduction was significantly greater in the dietary group. After 60-months follow-up, breast cancer relapse rates were significantly lower in the intervention group (p=0.03). This difference was even greater in the ER negative subgroup (p=0.018). There was a statistically significant improvement in overall survival in the intervention arm, although this was only statistically significant for specific breast cancer recurrence in women oestrogen receptor negative (Chlebowski et al., 2005).

Data from a longitudinal study of 335 patients from the University of Illinois was published in the Journal of the American dietetic association 2010. It looked at the self-reported, pre-diagnosis diets of women who had epithelial ovarian cancer. A diet high in fruits, vegetables, and healthful grains was associated with higher survival rates after treatment. The study also showed that consumption of less healthful meats was associated with a shorter survival time, although no correlation was noted for white meats and fish. Notably, there was also more risk associated with consumption of milk and milk-based foods.

Individual Components of Diet and their Mechanisms of Action:

The studies summarised so far report the influence of an overall change in diet, often described as prudent as opposed to western. Published studies relating to benefits or risks of individual components of diet after cancer are more difficult to conduct and are consequently less robust, but evidence can be extrapolated from cohort studies correlating lifestyle with cancer prevention. This is a reasonable assumption as the same factors increasing the risk of cancer are likely to increase the risk of relapse and, furthermore, cancer survivors have a greater risk of second cancer. Nevertheless, recommending advice based an extrapolated data or small trials should be made with caution until further specific randomised data is available. The remaining dietary section will review the available data for specific dietary components and discuss the underlying theoretical mechanisms of interaction with the cancer processes.

Cruciferous Vegetables

Broccoli and other cruciferous vegetable contain anti-carcinogenic isothiocyanates (ITCs), particularly the potent sulforaphane, which may decrease risk of cancer through induction of phase II enzymes, including glutathione S-transferases (GSTs). A population-based, case-control study evaluated this hypothesis in men with incident prostate cancer (n = 428) and community controls (n = 537). An in-person interview included an extensive food-frequency questionnaire. Intakes of cruciferous vegetables and broccoli, the greatest source of sulforaphane, were associated with decreased prostate cancer risk at all levels above the lowest consumers. These findings suggest that two or more servings per month of cruciferous vegetables may reduce risk of prostate cancer (Joseph et al., 2007).

Healthy Fats

Evidence from two large prospective studies (Augustsson et al., 2003; Terry et al., 2001) and a smaller case-control study (Norrish et al., 1999) suggests a protective effect of oily fish

intake on cancer incidence and mortality (Terry, Rohan, and Wolk, 2003). A unique nutritional component of fish is the long-chain marine omega-3 fatty acids. Cell line xenografts and small human studies have suggested that marine omega-3 fatty acids or the ratio of marine omega-3: omega-6 fatty acid can modulate the cyclooxygenase-2 pathway, a potential route for prostate cancer development (Chaudry et al., 1994). Laboratory experiments have also demonstrated that oleic acid helps repair DNA damage caused by excessive sunlight. This DNA repair affect is the reason olive oil is being used more frequently in skin care products, particularly 'after sun.' Furthermore, olive oil has been shown to suppress over-expressed Her-2 protein on breast cancer cells (Flowers and Thompson, 2009).

Natural Dietary Salicylates

Individuals with diets rich in fruit and vegetables, particularly vegetarians, have nature serum salicylate levels equivalent to a dose of 80mg of acetyl salicylate (aspirin) a day. This is more than enough to reduce the conversion of arachidonic acid to prostaglandins via the Cyclo-oxidase (COX) pathway**.** Many tumours over-express COX-2, particularly those with a more aggressive phenotype or those which have become resistant to hormonal therapies (Blacklock et al., 2001). In vitro, inhibitors of COX-2 such as non-steroidal anti-inflammatory drugs (NSAID) have been shown to induce apoptosis, inhibit proliferation, impair adhesion and signal angiogenesis in cancer cell lines and xenographs (Hsu et al., 2000). Prospective studies, including a COCHRANE meta-analysis, have shown a reduced incidence of malignancy associated with regular aspirin use (Egan et al., 1996; Fuchs et al., 2005; Schreinemachers and Everson, 1994). A prospective randomised clinical study showed a protective benefit against recurrent bowel cancer in patients taking aspirin (Mahmud, Franco, and Aprikian, 2003). Aspirin, however, can cause gastrointestinal upset and the third generation non-steroidal anti-inflammatory drugs have cardiac and renal safety issues (Dieppe, Ebrahim, and Juni, 2004; Hippisley-Cox and Coupland, 2005). High fruit and vegetable intake on the other hand is associated with lower GI morbidity and does not have any adverse effect on the kidney – clearly a much safer way to increase salicylate intake.

In an observational study published in the Journal of Clinical Oncology in 2010, researchers evaluated 4,164 women who had been diagnosed with early breast cancer. They found that those women who just happen to be taking aspirin, somewhere between two and five days, had a reduction in dying of the breast cancer. More specifically, although in women who took aspirin just once a week, there was no benefit, those who took aspirin two to five times a week experienced a 71 percent reduction in the risk of dying from a return of the cancer.

Carotenoids and Vitamin A (Retinol and Beta-Carotene)

Lycopene is a naturally occurring pigment found in tomatoes, chillies and other colourful fruits. As well as inducing antioxidant enzymes, there is growing evidence related to cell differentiation and proliferation independent of this mechanism of action (Stivala et al., 2000). Lycopene has been shown to have a protective benefit on prostate cancer risk among U.S. health professionals (Giovannucci et al., 2002). For men with established cancer, a small

non-randomised study looked at lycopene intake prior to prostatectomy and demonstrated less aggressive parameters compared to controls (Chen et al., 2001; Kucuk et al., 2002). Vitamin A is a fat-soluble essential vitamin found in fish, particularly cod liver and dairy food in the preformed isoform retinol. Beta-carotene is a pro-vitamin A found in carrots, green leafy vegetables and colourful fruits. Cancer cell line data have demonstrated an increased apoptosis and reduced proliferation when exposed to synthetic retinoids such as fenretinide (Hsieh and Wu, 1997). However, trials of supplemented beta-carotene in patients at high risk of lung cancer showed an elevated risk of lung and prostate cancer (Heinonen et al., 1998). Another large chemo-prevention study combined beta-carotene with retinol (Vitamin A) and showed a lower risk of prostate cancer in those with pre-intervention low plasma levels of beta-carotene; those with high levels had a higher risk (Omenn et al., 1996).

Antioxidants

Dietary antioxidants are thought to wield their anti-cancer properties by directly or indirectly counterbalancing the superoxide free radicals produced from our diet or other environmental factors (Chen et al., 2001; Giovannucci et al., 2002; Giovannucci et al., 2006; Stivala et al., 2000). Although patients with established cancer have already sustained DNA damage in order to mutate from benign to malignant cells, avoiding further DNA insult may avoid further mutation of indolent malignant or pre-malignant cells into more aggressive phenotypes (Chan, Gann, and Giovannucci, 2005; Sonn, Aronson, and Litwin, 2005; Wilkinson and Chodak, 2003). Otherwise known as free radical scavengers, they are found in a wide variety of dietary sources (Chan, Gann, and Giovannucci, 2005; Chlebowski et al., 2005).

The largest group of antioxidants are the non-oestrogenic phytochemicals or polyphenols, which include the phenolic acids, namely benzoic acid (hydroxybenzoic acid, gallic acid) and cinnamic acid (caffeic and quinic acid), together with the non-oestrogenic flavanoids including anthocyanidins, the flavanols (catechins and proanthocyanidins), lignans and stilbens (Chan, Gann, and Giovannucci, 2005; Sonn, Aronson, and Litwin, 2005; Wilkinson and Chodak, 2003). These phytochemicals do not act via a hormonal route, but have been shown to have some direct anti-oxidative, anti-proliferative activities (Wilkinson and Chodak, 2003). Kaempferol, found in teas and kale, has particularly been shown to reduce the risks of ovary and breast cancer within the ongoing Nurses' Health Study. These and other phytochemicals are also commonly found in flaxseed, linseeds, nuts, dark greens, cruciferous vegetables, prunes, brightly coloured vegetables, fruits and grains. Antioxidants can be found in less obvious sources such as coffee and chocolate (Svilaas et al., 2004), apples used for cider, and the tannin component of red wine (Schoonen et al., 2005). The FDA have published league tables relating to foods ability to induce these defence enzymes, known as their Oxygen Radical Absorbance Capacity (ORAC) (FDA, 2006).

A study from Australia demonstrated a relationship between antioxidant intake and cancer development. Individual presenting between 1996-2004 with SCC or BCC's were followed up with dietary questionnaires. The number of subsequent skin cancers were recorded. Those who had a higher intake of antioxidant rich foods had a statistically lower rate of new skin

cancer formation. The association was particularly strong in those with High Lutein zeaxanthin (leafy green vegetables). Interestingly individuals who had higher risk beta carotene and Vit E in supplement form had a higher rate of new cancer formation.) Heinen et al)

Phytoestrogens (Oestrogenic Phytochemicals)

These include flavones, isoflavones and flavanones, which are derived in the human diet mainly from soy beans and legumes including peas, lentils and beans (Wilkinson and Chodak, 2003). Dietary intake, for example, could potentially create a more favourable hormonal milieu for men with prostate cancer by inhibiting 5 alpha-reductase, the enzyme responsible for converting testosterone to the more active metabolite dihydrotestosterone (Evans, Griffiths, and Morton, 1995).

The benefits or risks of phytoestrogens on breast cancer have not been quantified but a clear pattern is emerging form the scientific data. At sensible doses phytooestrogens attach to the ER but only have weak oestrogenic activity. They dilute the effect of their own body's oestrogen. Genestein attaches to the ER in the same way as tamoxifen – inhibiting the oestrogen effect on tumours, but stimulating the bones and uterus. If excessive phyto oestrogens are then taken particularly in the form of extracted chemical extracts the oestrogenic effect can become too strong and the oestrogen receptor can start to be stimulated. This was highlight in an experiment with monkey's who were given a high dose phytoestrogen extract. After several months uterine hyperplasia developed. In humans eating sensible amounts, the overall effect is likely to beneficial after cancer - The largest population study in the world so far was called the Shanghai Breast Cancer Survival Study and involved 5,042 Chinese women patients who had completed treatments for breast cancer. Those with the highest intake had a 29% lower risk of death.

In the UK the issue of phytoestrogen intake may be solved by an ongoing national NCRN *DietCompLfy* study, which is correlating the risks of breast cancer relapse with levels of phytoestrogenic intake (Leatham and Velentzis, 2006).

Caution should be taken with excessive antioxidant intake, especially in supplement form, during chemotherapy or biological therapies. Antioxidant polyphenols in green tea may potentially decrease the efficacy of the cancer drug bortezomib (Velcade) and other boronic-acid proteasome inhibitors (Golden et al., 2009). Among the most widely used herbal supplements is St John's Wort (Hypericum perforatum), believed to have anti-depressant properties. This interacts with the liver enzyme (CYP3A4), decreasing the concentration of the chemotherapy drugs irinotecan, docetaxol and the biological agent imatinib (Scripture and Figg, 2006). Although the evidence for a number of other supplements is less robust, potential interactions have been reported with Echinacea, grape seed and gingko. Ephedra can increase blood pressure during cancer therapies and can compromise biological agents such as sutent and nexavar, and kava-kava can increase the risk of liver damage.

Vitamin C

Vitamin C has been shown to prevent the inhibition of gap-junction intercellular communication (GJIC) induced by toxic products such as hydrogen peroxide. Inhibition of

GJIC is related to carcinogenesis and tumour promotion (Lee, 2002). Vitamin C is involved in the mechanism which enables DNA to 'sense' free radicals by integrating with the iron imbedded in DNA, thereby facilitating DNA repair. It is therefore an important factor in immune surveillance against cancer as, according to estimates, each cell in the body can be expected to suffer approximately 100,000 DNA-damaging events per day (Fraga, 1991). A prospective double blind randomised trial involving men with progressive prostate cancer (*n* = 110) showed no difference in PSA doubling time in those given Vitamin C, magnesium, and copper gluconate or placebo (Thomas et al., 2005).

Vitamin D (and Sun Exposure)

Vitamin D is converted to the active metabolite calciferol in the kidney. Calciferol exposed to cancer cell lines reduces proliferation, promotes differentiation, inhibits invasion and loss of adhesion (Campell et al., 1997; Peehl et al., 1994; Schwartz et al., 1994), and promotes apoptosis (Blutt et al., 2000). It has also been shown to interact with the androgen signalling pathway in vivo inhibiting angiogenesis (Hsieh and Wu, 1997; Zhao et al., 1999). Eighty percent of humans' Vitamin D intake is generated via sunlight on skin, however, solar radiation is a well-established skin carcinogen, responsible for more cancers worldwide than any other single agent. The risk of skin cancer is particularly associated with sun burning and high sun exposure at an early age (Nyugen and Ho, 2002). More recently, there have also been concerns raised about the increasing use of artificial sun beds following the publication of an overview that analysed twenty studies which showed that the risk of skin cancer jumped by 75% when people started using tanning beds before age 30 (Cheng, 2009).

Although the risk of skin cancers increases with sun exposure, particularly burning, paradoxically the risk of cancers relapsing after initial therapy may be helped by sensible regular sun exposure, as demonstrated in the following studies.

A case controlled study from Sweden and Denmark analysed sun exposure habits of patients with lymphoma (*n* = 3,700) and controls (*n* = 3,200). The risk of lymphoma was significantly lower among people reporting prior regular sun exposure (Smedby et al., 2005).

The pathologist Berwick noted that subsequent mortality from melanoma was approximately one-half as high among those with other signs of sun exposure based on the histological specimen. Based on this premise, the same author went on to evaluate patients who had been surgically treated for localised cutaneous melanoma (*n* = 528). They were followed for an average of 5-years and levels of sun exposure were estimated by regular in-person interviews. A multivariable analysis showed that regular sun exposure was significantly associated with an inverse risk of death from melanoma (Berwick et al., 2005).

Vitamin D levels were measured in stored blood of women with early breast cancer (*n* = 512), diagnosed between 1989 to 1996. Vitamin D levels were found to be deficient (< 50 nmol/L) in 37.5% of patients, insufficient (50 to 72 nmol/L) in 38.5% of patients, and sufficient (> 72 nmol/L) in 24% of patients. The mean follow-up was 11.6-years; 116 women had distant recurrences, and 106 women died. Women with deficient vitamin D levels had a significantly

increased risk of distant recurrence compared with those who had sufficient levels (Goodwin et al., 2009).

Pre-diagnosis levels of 25(OH)D were measured in a cohort of participants in the Nurses' Health Study (n = 304) and the Health Professionals Follow-Up Study (HPFS) who were diagnosed with colorectal cancer from 1991 to 2002. Higher plasma vitamin D levels were associated with a significant reduction in overall mortality (Ng et al., 2008)

Vitamin E

Vitamin E in its eight naturally occurring isoform-tocopherols (Wilkinson and Chodak, 2003) has been linked to a reduction in cancer risk (Chan, 1999). The Alpha-Tocopherol Beta-Carotene cancer prevention study trial (ATBC), involving 29,133 male smokers, reported a statistically significant reduction of prostate cancer incidence and mortality although the primary end point of lung cancer was higher (Heinonen et al., 1998). In the Health Professionals Follow-Up Study (HPFS), vitamin E intake was also associated with decreased risk of prostate cancer in smokers, but not overall (Chan, Gann, and Giovannucci, 1999). The serum based Cancer Prevention II (CPII) Nutrition Cohort study showed an inverse correlation between plasma vitamin E levels and prostate cancer, again mainly among smokers and mostly the gamma-tocopherol isoform, which is primarily found in the diet rather than over the counter supplements (Rodriguez et al., 2004). In a further trial involving 39,876 patients with diabetes or cardiovascular disease, alpha-tocopherol demonstrated no reduction in cancer, and the incidence of heart disease was slightly worse (Lee et al., 2005). Likewise, in the ATBC study cerebral haemorrhage risk was also higher in smokers with hypertension who took alpha-tocopherol. Finally, the National Cancer Institute's sponsored double-blind randomised SELECT study showed no benefit of supplementary selenium and vitamin E over placebo to prevent prostate cancer (Klein, 2009).

Vitamin B12 and Folic Acid

Ebbing et al. (2009) evaluated the effects of treatment with B vitamins on cancer outcomes and all-cause mortality in two randomised placebo controlled trials in patients with ischemic heart disease (n = 6,837). The Norwegian Vitamin Trial and Western Norway B Vitamin Intervention Trial randomised men to oral treatment with folic acid (0.8 mg/d) plus vitamin B_{12} (0.4 mg/d) and vitamin B_6 (40 mg/d) (n = 1,708); folic acid (0.8 mg/d) plus vitamin B_{12} (0.4 mg/d) (n = 1,703); vitamin B_6 alone (40 mg/d) (n = 1,705); or placebo (n = 1,721) between 1998 – 2005. After a median 39-months of treatment and an additional 38-months of post-trial observational follow-up, 341 participants (10%) who received folic acid plus vitamin B_{12} versus 288 participants (8.4%) who did not receive such treatment were diagnosed with cancer. Results were mainly driven by increased lung cancer incidence in participants who received folic acid plus vitamin B_{12}; vitamin B_6 treatment was not associated with any significant effects (Ebbing et al., 2009).

A separate study found that those men who took folic acid supplements were more than twice as likely to develop prostate cancer, compared with men who took a placebo. Researchers note that the estimated prostate cancer risk was 9.7% for participants in the folic acid group

and 3.3% for the placebo group. They also found, however, that prostate cancer incidence was slightly lower in men who had adequate amounts of folate in their diet (Figueiredo et al., 2009).

Essential Minerals

Dietary trace elements, classified as antioxidants because manganese, zinc and copper are essential for the production of superoxide dismutase (SOD) and selenium is essential for glutathione peroxidase (Wilkinson and Chodak, 2003). Together with catalase these form enzymic defence against carcinogenic oxygen reduction metabolites (Marklund et al., 1982). It has been postulated that intensive farming food techniques and food processing may reduce these trace metals in our diet (Coombs, 2004; Jackson et al., 2004). There is evidence of an increased risk of carcinogenesis in the presence of copper, selenium manganese or zinc deficiencies, particularly under conditions of high carcinogenic attack where more SOD is needed (Chan, Gann, and Giovannucci, 2005; Sonn, Aronson, and Litwin, 2005; Wilkinson and Chodak, 2003; Levieux, 1991; Merli et al., 1995).

Human prostate cell lines have demonstrated greater growth inhibition with normal selenium compared to controls deficient in selenium (Mehta and Moon, 1991). Two large studies in 1980 and 1990 showed that a low selenium status was associated with an increased risk of developing cancer (Kok et al., 1987; Knekt et al., 1990). They also showed that in-patients with selenium deficiency, the cancer they developed were more likely to be more aggressive and fatal. The Harvard Health Professional Survey, for example, linked low selenium status (measured on toenail clippings) with higher rates of Gleason 8 and 9 prostate cancers. Both Finnish and Taiwanese studies have linked lower blood levels of selenium with higher rates of lung and hepatocellular carcinoma (HCC). In China, where the incidence of HCC is high, the inhabitants of one village were supplemented with sodium selenite whilst another five villages were given simple salt. After six years, involving over 130,000 people, there was a 35% reduction in the HCC rate in the selenium-supplemented village, but no change in the others (Blot et al., 1993).

A double-blind trial evaluated the benefits of dietary selenium. The primary end point, non-melanoma skin cancer, was not reduced but the incidence of prostate cancer was significantly reduced (Clark et al., 1998). The large SELECT study published in 2009 demonstrated that supplementing selenium and vitamin E did not show any reduction in the risk of prostate cancer (Klein, 2009).

Calcium

Four prospective cohort studies relating calcium and prostate cancer have been published (Sonn, Aronson, and Litwin, 2005). Two studies with a mean calcium intake of between 1330-1840mg/day showed no associated risk. Two others, one involving 86,404 men in the CP II nutrition cohort, with mean intake of >2000mg/day from food and supplements, showed a significantly higher risk of prostate cancer (Rodriguez et al., 2004). Five of nine further questionnaire surveys associated high intake of dairy food with increased risk of prostate and breast cancer, but in these surveys high dairy was associated with high fat intake (Sonn,

Aronson, and Litwin, 2005). Excessive dietary calcium reduces vitamin D, which has demonstrated anti-proliferative benefits that in theory are therefore lost with excess calcium (Campell et al., 1997).

Carcinogen Avoidance

Dietary or inhaled chemicals such as polycyclic aromatic hydrocarbons and aromatic amines, found in super-heated processed or fried foods, are converted to products which can directly or indirectly oxidise water or oxygen into short lived but highly energetic free radicals. These cause double or single DNA strand breaks, allowing cancer promoting genes to escape from the influence of their suppressor gene guardians (Chan et al., 2005). Numerous environmental studies have linked carcinogens to cancers and the USA Food and Drug Association (FDA) regularly publishes lists of foods containing high levels of acrylamides and other potential carcinogens such as pesticides, toxic additives, and chemical contaminants (FDA, 2006). Avoiding carcinogens may, therefore, have a benefit in reducing the risk of developing further cancers in patients who may be more susceptible from a pre-existing genetic signature or damage from chemotherapy or radiotherapy. This theory is supported by data from patients surviving the Hiroshima and Nagasaki bombings. A comprehensive medical follow-up of survivors of the atomic bombings by the Radiation Effects Research Foundation (RERF) showed that those who undertook regular exercise and had a higher intake of fruit and vegetables had a significantly lower risk of cancers despite their acquired susceptibility (Land, 1995).

Other environmental chemicals may have an adverse affect on cancer because of their oestrogenic properties, either because they have a chemical structure similar to oestrogen or affect the sex hormone activity in an indirect pathway. The most common group of chemicals are the polychlorinated biphenyls (PCB) and organochlorines found in sources which include pesticides, herbicides, car pollution, fuels, drugs and polycarbonate plastic baby bottles and food containers. It is difficult to prove harm in humans but five separate laboratory studies that have demonstrated that oestrogenic pollutant given in higher quantities to laboratory mice, induce and promote mammary cancers the same (Kortenkamp, 2008). A further study in 1993 showed that rhesus monkeys developed a thickened uterus (the first stages to develop cancer) and endometriosis after being fed food that contained dioxin, a xenoestrogen, over a four-year period (Rier et al., 1993). A class of preservatives found in some deodorants and cosmetics are called parabens, which in the laboratory have also been found to have harmful xenoestrogenic properties. An initial concern in humans was raised following a study in 2004 from Reading University, UK, which demonstrated higher quantities of parabens in the outer part of the breast and within breast cancer cells themselves. Although a direct link with cancer is not proven it did encourage many manufacturers to remove parabens from their products, but in some items they can still be seen on the label. Aluminium salts are responsible for the anti sweating affect of anti-sweating affect of anti-perspirants. A study in 2007 from Keel University, UK, created a lot of media activity when it showed higher quantities of aluminium in the upper outer area of the breast in those who used antiperspirants regularly. Aluminium has also been shown to have harmful oestrogenic properties when tested in the laboratory and consequently comes under the classification of metaloestrogens. It would be difficult to

design a human study to find out if regular antiperspirant users have a higher risk of breast cancer, but their presence in breast tissue is concerning particularly as exposure in some women can be daily for many years.

Adiposity

There is strong evidence that overweight individuals have a higher risk of cancer and a higher risk of cancer-related deaths. For example, the Million Women's study showed a direct correlation between BMI and endometrial, post-menopausal breast cancer, kidney, myeloma, pancreatic, ovarian and colorectal cancer (Reeves et al., 2007).

After a diagnosis of cancer and following its treatments, associations of obesity and outcome after cancer treatments have been observed for colorectal cancer (Haydon et al., 2006; Meyerhardt et al., 2005), but also for breast (Holmes et al., 1999; Holmes et al., 2005) and prostate (Giovannucci et al., 2006) cancer, with the improvement in survival being a result of decreased cancer and non-cancer related weight loss (Amling et al., 2004; Chlebowski, Aiello, and McTiernan, 2002).

The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial analysed 4,288 patients between 1989-94 and showed that very underweight (BMI < 19) and obese (BMI > 35) colon cancer patients had worse overall survival than healthy weight patients. This was due to greater risk of cancer recurrence as well as non-cancer deaths (Dignam et al., 2006).

Similar findings were demonstrated in a retrospective analysis of men with prostate cancer (n = 1,069), treated at the Cedars-Sinai Medical Centre Los Angeles between 1994-2002; obese men had a higher risk of early disease recurrence (Gross et al., 2006).

Li C et al. (2009) examined a cohort of 365 women with ER+ve breast cancer who had later developed a contralateral breast cancer. He compared their lifestyles with 726 matched controls. Obesity (BMI > 30kg/m^2), consumption of >7 alcoholic beverages a week, and smoking were all positivity associated with the risk of a contralateral cancer, with an odds ratio of 1:4.

Kroenke CH, et al performed a further analysis of the Nurses Health Study looking at weight gain after breast cancer treatment. 5204 registered nurses participated in the questionnaire survey between 1976-2000. There were 860 deaths (553 from breast cancer) on subsequent follow up. A high BMI at diagnosis correlated with an overall worse survival but a correlation with breast cancer relapse was only seen in non-smokers. Of more clinical relevance was weight gain after breast cancer treatments have finished. Weight gain more than 0.5kg/m^2 at 1yr correlated both with overall survival and breast cancer specific survival and the correlation was strongest in women who gained >2kg/m^2.

The mechanism of risk of being overweight for breast and endometrial cancer may lie in their higher oestradiol levels, which have been reported to reduce following weight reduction programmes (Wu et al., 1999). Diet may also influence hormone production and metabolism by a direct action and not via obesity; case-control studies have shown that diets low in fat

and high in fiber are associated with a high excretion of estrogen in the urine independent of their adiposity (Adlercreutz, Fotsis, and Bannwart, 1986; Rose, 1992).

Leptin - This is a multifunctional neuro-endocrine hormone generated primarily from fat cells. There is a direct correlation with the amount of body fat levels and circulating blood levels of leptin. There is also a correlation between leptin and serum insulin, IGF-1 and progesterone levels. Leptin has been shown in several laboratory experiments to promote proliferation, reduce apoptosis and reduce the 'stickiness' of cancer cells encouraging them to spread and metastasise. Higher leptin levels are associated with higher expression of Cycloxidase 2 which also, as described below, encourages cancers to grow faster and to spread.

Progesterone - Another important hormone affecting overweight women is progesterone. Compared to women with pre-menopausal 'normal' weight, obese women in particular have reduced serum progesterone. There is a significant body of evidence demonstrating that progesterone plays a protective role in cancer progression, particularly in the ovaries. Progesterone increases in pregnancy, which also adds some protection against breast and ovarian cancer. In post- menopausal women who are not overweight (BMI < 35kg/m^2), the evidence is less clear. The risk of breast cancer, in one large study from Sweden, was higher in women taking HRT containing progestin, than those containing oestrogen alone. On the other hand, another study of post-menopausal women with breast cancer from Boston, USA, women with higher blood levels of oestrogen and androgens had a worse prognosis, but no such correlation was found with progesterone. It may well be therefore, that the protective affect of progesterone is greater in pre-menopausal women.

Physical Activity

There is no doubt from the published literature that regular exercise, independent of other risk factors such as obesity and diet, reduces the risk of cancer. The most convincing evidence for this comes from the European Prospective Investigation into Cancer and Nutrition, where 218,169 pre-menopausal and post-menopausal women from nine European countries were evaluated for a median of 6.4-years. During this time, 3,423 incidents of invasive breast cancers were identified. High non-occupational , household and recreational physical activity were significantly associated with reduced breast cancer risk, independent of other potential risk factors such as educational status, BMI, smoking, alcohol use, age at menarche, age at first pregnancy, parity, current oral contraceptive use, and hormone replacement therapy use (Lahmann, 2007).

Although no conclusive randomised data has been published, the benefit of physical activity after a diagnosis has been established by a number of large and convincing cohort studies. Irwin et al. (2008) investigated a cohort of breast cancer survivors (n = 933) and found that

those who consistently exercised for more than 2.5 hours a 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 the women in the of the Nurses' Health Study (n = 2,987) and found that women with breast cancer who were walking > 3 hours a week at an average pace had lower recurrence rates and better overall survival than those engaged in less exercise.

Holick et al. (2008) performed a prospective observational study of breast cancer survivors (n = 4482) and found that women who were physically active for more than 2.8 hours a week had a significantly lower risk of dying from breast cancer (35-49% reduction) compared to those who were less active.

Pierce et al. (2007) published similar results but looked at the combination of diet and exercise among women who had been treated for breast cancer (n = 1,490). Women who ate five or more servings of fruit and vegetables a day and were physically active for at least 30-minutes 6-days a week had a higher 10-year survival.

Haydon et al. (2006) highlighted the benefits of exercise after a diagnosis of colorectal cancer (n = 526). There was a 31% reduction in cancer deaths for the physically active compared with the physically inactive across all stages. The benefit was greatest for stage II and III disease, with a hazard ratio (HR) for CRC-specific survival of 0.49 (adjusting for age, sex, and stage) in this subgroup. The CALBG 89803 study demonstrated a similar finding in which patients with stage III colorectal cancer (n = 816) completed detailed lifestyle questionnaires during and after adjuvant chemotherapy. Increased physical activity was associated with improved disease free survival (DFS) and overall survival (OS). In practical terms, this equated to a 35% improvement in disease free survival for individuals in the highest quintile of regular physical activity compared with the lowest quintile (Meyerhardt et al., 2005).

Friedenreich CM et al 2009 from Alberta conducted a randomized trial in 320 postmenopausal women, ages 50 to 74 for one-year. 160 women were randomly assigned to 225 minutes a week of aerobic exercise, the remaining 160 maintained their usual level of activity. At baseline, six months, and 12 months, the researchers assessed circulating levels of estrone, estradiol, androstenedione, and testosterone by radioimmunoassay and sex hormone-binding globulin (SHBG) by an immunometric assay. At the beginning, most of the women were overweight, with an average body mass index of about 29.

The intervention consisted of a monitored, structured program of at least 45 minutes of aerobic exercise five days a week for 12 months at 70% to 80% heart rate reserve. At least three sessions per week were done in a fitness facility with onsite exercise trainers and the remainder were home-based. The exercise was recorded on weekly logs and the average exercise achieved was 3.6 sessions a week, for an average exercise duration of 178.4 minutes

a week which corresponded to an average estimated energy expenditure of 5.7 metabolic equivalent-hours.
At the end of the trial, the researchers found moderate reductions in weight in the exercsise group. They also found significant reductions in serum estradiol and free estradiol (with treatment effect ratios of 0.93 and 0.91, respectively) for the exercisers compared with the controls. After adjusting for weight lost during the program, the changes in estradiol and free estradiol remained significant (at P=0.014 and P=0.006, respectively). There were no significant differences in estrone, androstenedione, and testosterone levels.

Mechanisms of Benefit: Theories behind the mechanisms of benefit found with physical activity include alterations in prostaglandin levels/ratios and positive effects on the immune system (Meyerhardt et al., 2005; Quadrilatero and Hoffman-Goetz, 2003; Westerlind, 2003). For colon cancer, the traditional theory is that exercise may help by increasing the bowel transit time, reducing the time that potentially carcinogenic substances are in contact with the bowel wall (Knols, 2005), although more recently this effect has been questioned. More likely, exercise and diet help 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., 1997; Kristal et al., 2002).

Weight reduction: Several studies have demonstrated that lifestyle and exercise interventions can help achieve a better weight. Adiposity 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 cancer for overweight post-menopausal women but not pre-menopausal women. Fortunately, oestrogen levels have been shown to reduce, following weight reduction programmes.

Oestrodiol levels; Friedenreich CM et al 2009 found significant reductions in serum estradiol and free estradiol for the exercisers compared with the controls even after adjusting for weight lost during the program, the changes in estradiol and free estradiol remained significant (at P=0.014 and P=0.006, respectively). Dietary fats intake may also have an influence on oestrogen by a direct effect, and not via exercise or obesity. Animal and case-controlled studies have shown that diets low in fat and high in fibre are associated with a high excretion of estrogen in the urine, which lowers blood levels irrespective of the adiposity (Adlercreutz, Fotsis, and Bannwart, 1986; Rose, 1992).

Insulin-like growth factors (IGF); The most compelling evidence lies in the idea that physical activity exerts its beneficial effect via insulin-like growth factors (IGF) (Giovannucci , 2001; Kaaks et al., 2000; McTiernan et al., 1998). A number of cohort studies have shown an increased risk of cancer, particularly colorectal, with higher levels of insulin-like growth factor 1 (IGF-1) and C-peptide. An inverse relationship with insulin-like growth factor binding protein 3 (IGFBP-3) levels (Giovannucci et al., 2000; Ma et al., 1999; Ma et al., 2004; Nomura et al., 2003) has also been shown, although this effect has not been confirmed in all studies (Palmqvist et al., 2002; Probst-Hensch et al., 2001). The benefits of lowering

IGF-1 may be linked to its central role in growth regulation processes. The main stimulus for IGF-1 production comes from growth hormone (Kaaks and Lukanova, 2002). This stimulatory effect of growth hormone is modulated by insulin, which increases growth hormone receptor levels and in turn IGF-1 (Baxter and Turtle., 1978; Suikkari et al., 1988). Early studies have shown that after binding to its receptors, which are found on normal colonic mucosal cells as well as colon cancer cells, IGF-1 can stimulate cell proliferation, inhibit apoptosis (Yu and Rohan, 2000), and promote angiogenesis (Freier et al., 1999; Warren et al., 1996). In the circulation, as over 90% 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).

Smoking

Continuing to smoke after a diagnosis of cancer has been shown to increase risk of further neoplasm's, increase complications in surgery, radiation and chemotherapy, impair appetite and nutrition, and reduce survival (Yu et al., 1997). Of course, a randomised trial looking at disease-specific survival is not possible, but well conducted cohort studies are still convincing.

Yu et al. (1997) reported the largest study looking at the influence of continuing to smoke after cancer. This study was conducted in Japan, where the incidence of smoking is increasing. The authors evaluated 25,000 heterogeneous patients who had been treated for lung, breast, or colorectal cancer. It was reported that the 1.5 year survival of the people who continued to smoke was 44%, whereas in those who quit it was 55%.

Richardson et al. (1993) reported a retrospective study of patients with histologically confirmed small-cell lung cancer (n = 540), evaluating the outcomes of those who stopped smoking at time of diagnosis compared to those who did not. The relative risk of a second lung cancer was 11 (CI, 4.4 to 23) in the 70% who managed to quit smoking, whereas, in the 30% who continued to smoke, it was 32 (CI, 12 to 69).

Gritz, et al. (1993) and Ostroff et al.,(1995) demonstrated the same finding in two further retrospective studies evaluating outcomes following treatment for head and neck cancer. The chance of survival from their primary disease was double if smoking ceased compared to the 40% if they continued to smoke.

Li et al. (2009) examined a cohort of 365 women with ER+ve breast cancer who had later developed a contralateral breast cancer. He compared their lifestyles with 726 matched controls. Smoking, consumption of >7 alcoholic beverages a week and obesity were all positivity associated with the risk of a contralateral cancer (odd ratio 1:4).

Mechanisms of Harm: Continuing to smoke exposes the body to high levels of carcinogens, which can cause further DNA damage to existing cancers, encourage the cancer to mutate into a more aggressive type, or develop mechanisms to hide from the body's immunological defences. Patients who have already developed one cancer are likely to be more susceptible to DNA damage from a pre-existing genetic vulnerability, or acquired damage from chemotherapy or radiotherapy. Avoiding carcinogens may, therefore, have a benefit in reducing the risk of developing further cancers in patients who may be more susceptible from a pre-existing genetic signature or damage from chemotherapy or radiotherapy. There is also evidence that smoking reduces the effectiveness of some therapeutic agents. Smoke interferes with hepatic cytochrome P450 CYP1A, which has been shown to reduce bioavailability of erlotinib (tarceva) by 25% (Hamilton, Wolf, and Rusk, 2006). It also induces UDP-glucuronosyl transferase, important for conjugation of bile and conversion of Irinotecan to its

active component SN-38. Smokers have demonstrated 40% more serum SN-38 than non-smokers, which although lowering toxicity is also likely to lower effectiveness (van der Bol et al., 2007).

Alcohol

The link between intakes of alcoholic beverages was most clearly established by Allen et al. (2009) in the Million Women Study. Since 1996 this study has been gathering detailed information from 1.28 million women ages 50 to 64 years. Amongst other lifestyle factors, they examined how much alcohol women reported consuming when they volunteered for the study and again three years later, examining whether there was any link with the 68,775 cancers they developed over an average of the next seven years. There were statistically significant increased risks of cancer in those who regularly consumed alcohol. Another study by Thun et al. (1997) indicated that more than one drink a day increased the risk of breast cancer, but up to one drink was not associated with an increased risk (Thun et al., 1997). A further study from the University of California showed that men who drank heavily (> 50g of alcohol or four drinks daily) doubled their risk of high grade prostate cancers compared to other men. There was no difference in the incidence of low grade cancers, implying that drinkers have a poorer prognosis (Gong et al., 2009).

Schwartz et al. (2006) evaluated a cohort of survivors following head and neck cancer, recording alcohol intake for a median follow-up of one year. There was a significant difference in the rate of relapse, which in these cases almost entirely led to death. Survival in those who continued to drink excessively was 6% and in those who gave up or drank in moderation was 27%.

The evidence of alcohol and risk of relapse after breast and other cancers is less convincing. In fact, one study from the Catholic University and the National Research Council in Italy showed that a glass of wine a day may cut the risk of treatment-linked skin toxicity by two-thirds in women undergoing radiation therapy for breast cancer. They evaluated the drinking habits of women with breast cancer (n = 348) and found that patients who drank wine on the days they had their treatment had lower rates of Grade 2, or higher acute toxicity, than those who did not (13.6% rate of skin toxicity compared to 38.4%). This observation did beg the question that wine may also reduce the effectiveness of radiotherapy, but relapse rate was not measured in this study (Mundell, 2009).

Li et al. (2009) examined a cohort of 365 women with ER+ve breast cancer who had later developed a contralateral breast cancer. He compared their lifestyles with 726 matched controls. Consumption of >7 alcoholic beverages a week, obesity and smoking were all positivity associated with the risk of a contralateral cancer.

Mechanisms of Harm: The underlying factors which increase the risk of cancer are not fully understood, especially when it is known that some drinks contain antioxidants which in theory could help fight oxidative stress. One factor is that acetaldehyde is easily measured in the breath after drinking alcohol and this is a potent carcinogen. Alcohol intake has also been shown to increase endogenous oestrogen levels (Onland-Moret et al., 2005). Finally, alcohol is fattening and increases the risk factors of adiposity described above.

Conclusion and Recommendations **(Improving Cancer Outcomes)**

Understanding the clinical studies which attempt to investigate the interaction between specific aspects of lifestyle and cancer is also complicated by the caveat that health-seeking enthusiasts often follow a range of behaviours from exercise to dietary manipulation, smoking cessation, reduction in body size, supplements and analgesic intake, confounding the published data (Chan et al., 2005; Chlebowski et al., 2005; Sonn, Aronson, and Litwin, 2005). Furthermore, the mechanisms of the benefits of lifestyle are likely to be multi-factorial and additive (Thomas, Daly, and Perryman, 2000). Nevertheless, there is considerable evidence that lifestyle can improve clinical outcomes in respect to a reduced risk of progression in some men with prostate cancer, reducing the risk of relapse and improving the chance of survival. Evidence is strongest following breast, bowel, lung, head and neck cancers but self-management lifestyle strategies are likely to be person-specific rather than disease or treatment specific.

Further research is required, especially in the areas of levels of exercise and correction of nutritional deficiencies with specific supplements, but in the meantime, based on the available evidence, the following self-help lifestyle strategies can be safely recommended:

Exercise:

- Include more physical options as part of the activities for daily living (Appendix 1)
- Aim to regularly participate in at least 2.5 hours of vigorous exercise per week (Appendix 2)

Other Lifestyle Factors:

- Avoid obesity (BMI >35 Kg/m^2)
- Avoid being underweight (BMI <19 Kg/m^2)
- Limit or stop drinking alcohol
- Stop smoking, if relevant
- Take regular gentle sun exposure, without burning (Appendix 3)

Diet:

Aim for a healthy, varied diet avoiding fads and ensuring adequate intake of vitamins, essential minerals, fibre, essential fatty acids and antioxidants (Appendix 3):

- Eat more -
    - Green and cruciferous vegetables
    - Fruits and berries
    - Nuts and grains
    - Healthy oils; (unsaturated fats, omega 3)

- Eat less -
    - Unhealthy fats (saturated fats)

- Carcinogenic containing foods

Dietary supplements should not be required if individuals are able to eat a varied, balanced diet. This review found no evidence suggesting that they can improve cancer outcomes and, in fact, studies involving vitamin A and E have shown increased cancer risks as well as cardiac and cerebral vascular morbidity. There is evidence from cohort and prevention studies that individuals with vitamin or essential deficiencies benefit from specific nutritional supplements. These, however, are not measured in routine clinical practice but ideally, future trial designs should include bespoke patient analysis to identify those individuals with sub-clinical deficiencies.

PART TWO

Evidence for Lowering the Risks and Side-Effects during and after Cancer Treatments

Cancer-related Fatigue,

Body Composition,

Psychological Well-Being,

Quality of Life, Lymphoedema,

and Bone Health

Cancer-related fatigue

The National Comprehensive Cancer Network (NCCN, 2009) defines cancer-related fatigue (CRF) as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer-related treatment that is not proportional to recent activity and interferes with usual functioning.

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. This post-treatment fatigue syndrome can last for up to 12-months (Wagner and Cella, 2004; Thomas, 2005; NCCN, 2009). It is also reported in up to 40% of patients taking therapies required for longer periods of time, such as common hormone therapies (tamoxifen, aromatase inhibitors, goserelin), as well as being associated with monoclonal antibody therapy such as transulumab, citixumab and the tyrosine tynase inhibitors (Lucia, Earnest, and Perez, 2003; Wagner and Cella, 2004; Velthuis et al., 2009).

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. It can have a phenomenal impact on a patient's life, interfering with daily activities and also may potentially have devastating social and economic consequences. It can hinder a patient's chance of remission or even cure, owing to the effect it can have on the desire to continue with treatment (Lucia, Earnest, and Perez, 2003; Wagner and Cella, 2004; Thomas, 2005; Velthuis et al., 2009; NCCN, 2009).

The specific causes of treatment-related fatigue are not fully understood, but there are several associated conditions which can aggravate it. These include anaemia; drugs such as opiates, antihistamines, and anti-sickness medication; electrolyte imbalance; liver failure; steroid withdrawal; and, of course, sedatives (Thomas, 2005). Some conditions can also cause fatigue by disturbing a persons' sleep pattern, such as anxiety, depression, nocturia, night sweats and pruritis (itching). The first step to treating CRF is to correct, if possible, any of these associated conditions. Sleep hygiene advice is also recommended, but there is little evidence for its effectiveness. The self-help strategy most extensively investigated for CRF is exercise and the evidence for its benefit is described below.

This current review identified two records and initiatives in progress, which were categorised into one type of support for CRF: Exercise (e.g. Home-Based Exercise Programmes – Walking; Resistance Exercises; Aerobics; Seated Exercises; Supervised Exercise Programmes – Aerobics; Resistance Exercises; Stretching).

Evidence from Randomised Controlled Trials

There have been two recent meta-analyses addressing CRF and exercise interventions. The first, published in 2008, reviewed 28 RCT's (Cramp and Daniel, 2008) and the second, in 2009, from the Netherlands, reviewed 18 RCT's (Velthuis et al., 2009).

Cramp and Daniel (2008) conducted and published a Cochrane meta-analysis review, whereby twenty-eight studies were identified for inclusion (n = 2083 participants), with the majority comprising participants with breast cancer (n = 16 studies; n = 1172 participants). A pooled meta-analysis of all available data convincingly showed that exercise was statistically more effective in reducing CRF than the control.

Velthuis et al. (2009), from the Netherlands, conducted and published a second meta-analysis,where eighteen studies were reviewed (n = 1109 participants). Pooled results of all studies in breast cancer patients (n = 674 patients included in the analysis) showed a significant reduction of CRF in favour of the exercise group. During prostate cancer treatment, exercise also led to a significant reduction of CRF compared to the non-exercise intervention groups.

The 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 within specific supervised classes. Many of the interventions in this category include a combination of aerobic and resistance exercises.

Home-Based Exercise Programmes

Patients included in home-based exercise studies underwent hormonal therapy (Payne et al., 2008), radiotherapy only (Drouin, Krause, and Orr, 2005), chemotherapy only (Headley et al., 2004; Mock et al., 1994), and radiotherapy or chemotherapy (Mock et al., 2005; Payne et al., 2008). The overall finding was that during breast cancer treatment, home-based exercise led to a small, non-significant reduction in CRF.

In most studies, the home-based exercise intervention consisted of walking (Mock et al., 1994; Mock et al., 2001; Mock et al., 2005; Drouin, Krause, and Orr, 2005; Payne et al., 2008); in one study, combined with resistance exercises (Crowley, 2003). Patients walked between 3-6 times for 10-45 minutes per week. The intensity of exercise varied between: *"at own desired pace"* to 70% of maximum heart frequency (heart rate max) adjusted for age. In the only study in patients with advanced breast cancer, the home-based exercise programme consisted of seated exercises (Headley et al., 2004). Home-based exercise was mostly (in five out of seven studies) offered for the duration of radiotherapy (6-7 weeks) or chemotherapy (3-6 months) (Mock et al., 1994; Mock et al., 2001; Mock et al., 2005; Drouin, Krause, and Orr, 2005).

Seventy to 100% of the participants were reported, in these studies, to have completed the home-based exercises, indicating high compliance rates. Adverse effects were rare, with one patient in one study needing to stop the exercise programme due to over-exercising (shoulder tendonitis) (Drouin, Krause, and Orr, 2005).

The pooled results of two high quality studies out of seven studies describing a home-based exercise programme (n = 128 patients included in the analysis), showed a small, non-significant reduction in CRF (Drouin, Krause, and Orr, 2005). Data of three high quality studies (n = 84 patients in total) (Mock et al., 1994; Mock et al., 2001; Crowley, 2003) and two low quality studies (n = 50 patients in total) (Headley et al., 2004; Payne et al., 2008) could unfortunately not be included in the pooled analysis since data could not be obtained from the researchers.

Windsor, Nichol, and Potter (2004) published a study of 65 patients with prostate cancer receiving radiotherapy. Participants were randomly allocated a home-based exercise programme or standard supportive care. The home-based exercise included walking 30-minutes three times a week, with an intensity of 60%-70% heart rate max, for the duration of radiotherapy. No adverse events were reported and a non-significant reduction of CRF was found in the exercise group.

There has been one study in patients with multiple myeloma (Coleman et al., 2003), which included a home-based exercise programme during chemotherapy and peripheral blood stem cell transplantation. The exercise programme consisted of a combination of aerobic and resistance exercises, three times a week, 20-minutes, for the duration of the chemotherapy (± 6 months). No adverse events were reported and a small, non-significant reduction in CRF was found in the exercise group.

Supervised Exercise Programmes

Five RCTs included a supervised exercise programme in their design. In one study, patients were treated with radiotherapy only (Hwang et al., 2008) and in another with chemotherapy only (Courneya et al., 2007). In the remaining three studies, patients were treated with a combination of either radiotherapy only, chemotherapy only or both (Battaglini, 2004; Campbell et al., 2005; Mutrie et al., 2007; Battaglini et al., 2008).

Three supervised exercise interventions consisted of aerobic exercises (Campbell et al., 2005; Courneya et al., 2007; Mutrie et al., 2007). One intervention group included aerobic and resistance exercises and a control group (Courneya et al., 2007). Two studies combined aerobic exercises with stretching and resistance (Battaglini, 2004; Hwang et al., 2008). The exercise programmes were offered two or three times a week. Aerobic exercises were performed with an intensity of 40%-80% HR max adjusted for age for 10-30 minutes. The resistance exercises were performed with an intensity of 60-70% of one repetition maximum

(2 x 12 repetitions). In two studies, duration (15-30 minutes) instead of intensity of the resistance exercises was presented (Battaglini, 2004; Hwang et al., 2008).

The supervised exercise programme was completed by 79-100% of the participants. In only one of these four studies, two patients in total needed to stop the exercise programme due to adverse events, namely light-headedness and dizziness (Courneya et al., 2007). The pooled results of studies involving a supervised exercise programme showed a significant reduction in CRF in favour of the exercise groups.

The three studies in patients with prostate cancer investigated effectiveness of supervised exercise during radiotherapy and androgen deprivation therapy (Segal et al., 2003; Monga et al., 2007; Segal et al., 2009).

In two studies, patients allocated to the intervention group participated three times a week in a supervised exercise programme consisting of aerobic exercises with an intensity of, respectively, 65% of the maximum heart frequency (HR max) adjusted for age and 50%-75% of the VO2peak (15-45 minutes) (Monga et al., 2007; Segal et al., 2009). In the other supervised exercise programme, the intervention consisted of resistance exercises for two or three times a week with an intensity of two sets of 8-12 repetitions 60%-70% of the one repetition maximum (Segal et al., 2003).

Over 80% of the participants were reported to have completed the supervised exercise programme, however, the programme did result in one knee injury, chest pain, fainting, and an acute myocardial infarction.

Pooled results from the two supervised aerobic studies showed a large, non-significant reduction in CRF in favour of the exercise group (Monga et al., 2007; Segal et al., 2009). The resistance exercise study showed a small, non-significant reduction in CRF in favour of the resistance exercise group (Segal et al., 2003).

Chang et al. (2008) published a study involving patients with acute myelogeous leukemia (n = 22), which included allocation to the intervention group, a three-week supervised walking programme during chemotherapy. Participants walked five times a week for 12-minutes, in the hospital hallway. The supervised exercise programme was completed by 69% of the participants and no adverse events were reported. A medium-sized, non-significant reduction in CRF was found in the exercise group.

Conclusion and Recommendations (CRF)

Cancer-related fatigue is a significant problem for patients during and after their treatment. It is common to all cancer types and a wide range of therapies including post-surgery, radiotherapy, hormone therapies, but above all chemotherapy. It has a major impact on quality of life and psychological well-being. Several measures of CRF exist but the two emerging as the most reliable in the published literature are the EORTC QLQ-C30 or the

FACT-F (Minton and Stone, 2009). Fortunately, evidence from 28 RCT and 2 meta-analyses has demonstrated that intervention with exercise and lifestyle programmes can reduce the severity of CRF and its effect on QoL. The studies reviewed here also showed that supervised aerobic exercise programmes were more effective in reducing CRF during breast cancer treatment than home-based exercise advice. Adverse events during exercise were extremely low. Adherence was excellent for a supervised program (70-100%) and fair for a home exercise advice model (<40%), except for a walking programme (100%) although this did not demonstrate a significant benefit. Although more research on the optimal timing and duration of exercise would be useful, these studies are sufficiently robust to recommend:

- Patients with CRF, or at risk of it, should be advised on the benefits of exercise.

- Patients should be informed of local exercise facilities.

- Although there was clinical heterogeneity between published RCT's in terms of exercise duration, frequency and intensity, a sensible pragmatic approach based on the trials which showed most benefit, is to supervise a low to moderate intensity exercise regimen, regular frequency (3-5 times/week) for at least 20-minutes per session, involving aerobic, resistance, or mixed exercise types.

- Ideally, a local exercise programme should be established and managed by specifically trained exercise professionals.

- The responsible exercise professional should be sufficiently qualified to deliver an exercise programme which ensures the optimal level of supervised exercise. They should also be trained to deal with and be sympathetic to the overall needs of patients receiving or who have received cancer therapies.

- Further research is needed investigating the effects of exercise in patients with metastatic cancer as only one small RCT has been published in these patients.

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 (ref Thomas). 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, tend to overeat; others, with fatigue and nausea, stop exercising; and, drugs, including steroids and hormone therapies such as tamoxifen.

Exercise and Nutritional Counselling Strategies:

Whatever the reasons for weight gain, numerous reviews and meta analysis of the published literature have demonstrated significant reductions in obesity {Knols R, 2005 #93; Winningham M, 1989 #210, Iop et al., 2004, (Kim, Kang, and Park, 2009). These strategies, do not just improve weight but have significant other benefits on body constitution and fitness such a lean mass indices, bone mineral density, cardiopulmonary function, muscle strength and walking distance {MacVicar M, 1989 #211}. Examples of studies which evaluated the benefits of lifestyle and exercise on well being are described below:

Kim, Kang, and Park (2009) published a meta-analysis of 10 studies involving 588 women who had been treated for breast cancer, examining the effectiveness of aerobic exercise interventions on cardiopulmonary function and body composition, conducted during or after cancer treatments. They concluded that regular aerobic exercise significantly improved cardiopulmonary function as assessed by absolute VO_2 peak, relative VO_2 peak, and 12-minute walk test, as well as improved body composition as assessed by percentage body fat (although body weight and lean body mass did not change significantly).

Chlebowski RT et al, (2005) published the results of a RCT where 2,437 postmenopausal women with early breast cancer were randomised to nutritional and lifestyle counselling, or not, as part of routine follow-ups. The dietary intervention included eight bi-weekly individual counselling sessions. Dietary fat intake reduction was significantly greater in the dietary group. This major study also demonstrated a survival advantage in women who lost weight and is described again in Part 2 of this review.

Courneya et al. (2007) published a multicentre RCT in which women with breast cancer on adjuvant chemotherapy were randomly assigned to usual care (n = 82), supervised resistance exercise (n = 82), or supervised aerobic exercise (n = 78) for the duration of their chemotherapy (median, 17 weeks; 9 to 24 weeks). There was 70% adherence to supervised exercise. Aerobic exercise was superior to usual care for improving aerobic fitness and percent body fat, whilst resistance exercise was superior to usual care for improving muscular strength, lean body mass, and chemotherapy completion rate.

Schmitz et al. (2005) evaluated the safety and effects of twice-weekly weight training among 85 breast cancer survivors in an RCT. Women were randomised into immediate or delayed

treatment groups. The immediate group trained from months 0 to 12; the delayed treatment group served as a no exercise parallel comparison group from months 0 to 6 and trained from months 7 to 12. The intervention resulted in significant increases in lean mass, as well as significant decreases in percentage body fat. Only one participant experienced a study related injury that prevented continued participation.

Mefferd et al. (2006) specifically evaluated overweight or obese breast cancer survivors. Eight five women were randomly assigned to a once weekly, general exercise and dietary counselling for 16-week intervention or standard care. The intervention addressing a reduction in energy intake, as well exercise, with a goal of an average of one hour a day of moderate to vigorous activity. Seventy six women (89.4%) completed the intervention. At 16-weeks, significant group differences were evident in weight, body mass index, percent fat, trunk fat, leg fat, as well as waist and hip circumference. Levels of triglycerides and total cholesterol/high density lipoprotein cholesterol levels were also significantly reduced following the intervention.

Segal et al. (2009) conducted a RCT with 121 men with prostate cancer initiating radiotherapy with or without androgen deprivation therapy. They were randomly assigned to usual care, resistance exercise and aerobic exercise for 24 weeks. Median adherence to prescribed exercise was 85.5%. Compared with usual care, training improved aerobic fitness, upper- and lower-body strength, and triglycerides, while preventing an increase in body fat. Resistance exercise generated longer-term improvements and additional benefits for strength, triglycerides, and body fat. There were no reported adverse events in the exercise group.

Conclusion and Recommendations **(Lifestyle, Exercise and Body Constitution)**

Supervised exercise programmes with or without dietary counselling are highly effective in improving body constitution. What's more, they are safe and have other major benefits on health, including improving fitness, walking distance, muscle power, reducing cholesterol and high density lipoproteins. Compliance to supervised exercise programmes is high (72-86%). The following strategies are recommended:

- The benefits of exercise for weight reduction, muscle strength during and after cancer treatments should be counselled to patients and included in their multimodal information materials.
- Aerobic and resistance exercise should start during initial cancer therapies to prevent weight again and improve muscle strength.
- Supervised longer term aerobic and resistance exercise programmes should be locally available for patients and their relatives in groups or individually.

Table 2. Summarising Evidence for Exercise and Body Composition

Authors	Design	Cohort	Intervention	Outcome
Kim, Kang, and Park (2009)	Meta-analysis	Breast cancer	Aerobic exercise during or after treatment	SS better PBF and CPF
Chlebowski et al. (2005)	RCT (n=2467)	Breast cancer	Bi-weekly lifestyle and exercise counselling	SS better weight reduction and overall suvival
Courneya et al. (2007)	RCT (n=242)	Breast Cancer	Supervised aerobic and resistance training	SS better PBF, LBM and strength
Schmitz et al. (2005)	RCT (n=85)	Breast Cancer	Twice weekly Weight training classes	SS better PBF
Mefferd et al. (2006)	RCT (n=85)	Overweight breast cancer	Weekly exercise counselling 16 weeks	SS better weight, BMI, PBF, triglycerides and total cholesterol
Segal et al. (2009)	RCT (n=121)	Prostate cancer on radiotherapy	Resistance and aerobic exercise	Improved strength, body fat, triglycerides

SS – Statistically significant; BMI – Body Mass Index, LBM- Lean Body Mass; PBF-Percentage Body Fat; CPF – Cardiopulmonary function

Psychological Well-Being

Understandably, being diagnosed with cancer is a stressful experience and requires a high level of emotional and social readjustment (Holmes and Rahe, 1967). Whilst many people adjust well to a cancer diagnosis, prevalence rates of 25-30% for psychological distress are consistently reported (Deragotis et al., 1983; Farber, Weinerman, and Kuypers, 1984; Stefanek, Derogatis, and Shaw, 1987; Zabora, 1998; Zabora, 2001). Indeed, the first three months of a cancer diagnosis are thought to be the most distressing, evoking an 'existential plight' whereby an individual desperately seeks to make sense of their current circumstances (Mathieson and Stam, 1991; O'Connor et al., 1990). Still, psychological well-being, 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 (Mock, 1997; Mock, 2001). Continuing exercise into the follow-up period has also been show in women with breast cancer, who have demonstrated improved mood, happiness, self-esteem, and energy (Courneya, 2003; McKenzie, 2003; Pinto, 2003). Examples of studies evaluating the benefits of lifestyle on psychological well being are summarised below:

Hospital-Based Exercise Interventions after High Dose Chemotherapy

Dimeo et al. (1999) published a small RCT involving 59 cancer patients (breast, lung, non-Hodgkin's lymphoma) receiving high dose chemotherapy. They were randomised to an aerobic training group (n = 27) or control group (n = 32). The aerobic training group took part in an exercise programme during hospitalisation, comprising 'cycling' on an ergometer (allowing the simulation of the cycling motion without leaving the bed) following an interval training pattern: they cycled for one-minute with intensity sufficient to reach a heart rate equivalent of at least 50% of the cardiac reserve. This was repeated fifteen times with pauses of one-minute between; therefore, training was performed for a total of 30-minutes per day. During training sessions, patients were supervised by study personnel. By the time of hospital discharge, the training group reported significant improvements in psychological distress, particularly in regard to obsessive compulsive traits, fear, interpersonal sensitivity, and phobic anxiety.

Supervised Aerobic and Resistance Exercise during Chemotherapy

Courneya et al. (2007) evaluated 242 women in a prospective, three-armed, randomised controlled trial who had stage I to IIIA breast cancer and were beginning first-line adjuvant

chemotherapy. Participants were stratified by chemotherapy protocol (taxane based *v* non–taxane based) and randomly assigned to supervised aerobic exercise (AET; n = 82), supervised resistance exercise (RET; n = 82), or usual care (UC; n = 78) in a 1:1:1 ratio. Participants exercised for the duration of their chemotherapy (median = 17-weeks; 9-24 weeks), beginning 1-2 weeks after starting chemotherapy and ending 3-weeks after chemotherapy. Warm-up and cool-down periods were 5-minutes of light aerobic activity and stretching. The AET group was asked to exercise three times per week on a cycle ergometer, treadmill, or elliptical beginning at 60% of their maximal oxygen consumption, for weeks 1-6 and progressing to 70% during weeks 7-12 and 80% beyond week 12. Exercise duration began at 15-minutes for weeks 1-3 and increased by 5-minutes every 3-weeks until the duration reached 45-minutes at week 18. The RET group were asked to exercise three times per week, performing two sets of 8-12 repetitions of nine different exercises at 60% to 70% of their estimated one-repetition maximum. The exercises were leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, bicep curls, and modified curl-ups. Resistance was increased by 10% when participants completed more than twelve repetitions. The UC group was asked not to initiate an exercise program and was offered a 1-month exercise program after post-intervention assessments.

They reported that both aerobic and resistance exercise were superior to usual care for improving self-esteem and psychological functioning as measured by the Rosenberg Self-Esteem Scale; the Center for Epidemiological Studies Depression Scale; and, the Spielberger State Anxiety Inventory. They did not find that the exercise had an impact on QoL as measured by cancer-specific QoL (FACT-Anemia).

Self-Reported Exercise

Pinto and Trunzo (2004) report on a non-randomised cross-sectional study among 79 women treated for early-stage breast cancer in the past 5-years. The regular exercisers, who self-reported exercising vigorously three or more times a week for a duration of 20-minutes each time or moderately five or more times per week for a duration of 30-minutes each time, had significantly more positive attitudes toward their physical condition and expressed greater sexual attractiveness. They were also significantly less depressed and reported less total mood disturbance measured by the Body Esteem Scale and the Psychological outcomes Mood States (POMS).

Yoga

Rao et al. (2008) report a single-centre RCT involving 68 women with stage II and III breast cancer patients, to evaluate the effects of a yoga intervention versus supportive therapy and exercise rehabilitation on psychological well-being.

The intervention group received an 'integrated yoga program' and the control group received 'supportive counselling and exercise rehabilitation.' These sessions were administered by an instructor at the subjects' bedside prior to surgery and during their post-operative recuperation in the hospital. Following their discharge, subjects were asked to practise at home for the next four-weeks. Subjects were also provided audiotapes of an instructor's voice to help them practise at home so that a familiar voice could be heard on the cassette. Their practice was monitored daily by their instructor through telephone calls once a week. Subjects were encouraged to maintain a daily log listing the yoga practices done, use of audio-visual aids for practice, duration of practice, and experience of distressing symptoms. They reported a significant decrease in anxiety states, measured by the proxy of anxiety index (STAI), and improvements in QoL, assessed using the Functional Living Index of Cancer (FLIC) following surgery in the yoga group as compared to controls, but not in terms of depression. There was also a significant decrease in symptom severity in the yoga group as compared to the controls following surgery.

Lengacher et al. (2009) published a two-armed RCT with a total of 84 women previously diagnosed with Stage 0, I, II, or III breast cancer who underwent surgery and received adjuvant radiation and/or chemotherapy within the prior 18-months. They were randomised to a 6-week mindfulness-based stress reduction (MBSR), psychologist led intervention program of meditation and yoga or control group. The results of this study demonstrated that participants in the 6-week mindfulness-based stress reduction program reported significantly lower levels of depression, anxiety, and fear over recurrence than did usual care as measured by the Concerns about Recurrence Scale; State-Trait Anxiety Inventory; CES-D; Life Orientation Test; Perceived Stress Scale

Vadiraja et al. (2009) provide further support for the psychological benefits of yoga in an RCT involving 72 women recently diagnosed with stage II and III breast cancer who had undergone surgery as their primary treatment and were receiving adjuvant radiotherapy. The intervention yoga program comprised a combination of a set of *asanas* (postures done with awareness), breathing exercises, meditation and yogic relaxation based on principles of stimulation and relaxation. Participants were asked to attend a minimum of at least three in-person sessions per week for 6-weeks during their adjuvant radiotherapy treatment in the hospital, with self-practice as homework on the remaining days. Both intervention and control groups were offered supportive education and counselling by a trained social worker during radiotherapy and for 6 weeks after. The yoga group showed significant improvement in positive affect, decrease in negative affect, and improvement in emotional function as measured by the QoL scale EORTC QLQ-C30). There was also a significant positive correlation between positive affect and physical function (QoL domain).

Lifestyle and Nutritional Counselling (RCTs)

Scheier et al. (2007) evaluated the effects of lifestyle and teaching coping strategies in 252 women with early-stage (0-II) breast cancer within 2-months of having completed active non-

hormonal adjuvant therapy. They were randomly assigned to standard medical care or education and nutritional counselling. The education and nutrition participants received a series of four two-hour group sessions that met once a month for four consecutive months. They received information about their disease and treatment and were provided with a set of relevant coping skills, together with information on how to adopt and adhere to a low-fat, high-fruit and vegetable diet. They reported a significant impact, by the intervention, on the level of depressive symptoms, mental and physical health functioning (SF-36) and personality measures of dispositional optimism Life Orientation (Fritz and Helgeson Scale). The level of benefit was influenced by co-morbidities and social support measured by the *Unsupportive Social Interactions Inventory*. Those with negative social factors or co-morbidities had the greatest benefit.

Conclusion and Recommendations **(Psychological Well-Being)**

The benefits of physical activity, yoga, meditation and a healthy diet on psychological outcomes have been demonstrated in cancer survivors. The benefits apply to patients both undergoing active acute treatments including surgery, chemotherapy and radiotherapy as well as those in the "survivorship" period. The psychological benefits ranged from improved mood, affect, self-esteem to lower fear of recurrence, depression, and pessimism. Both aerobic and resistance exercises have demonstrated benefits in psychological outcomes with the evidence suggesting that survivors who exercise regularly for the long-term had the most benefit. Evidence from these studies indicates that vigorous exercise three or more times a week for a duration of 20-minutes each time or moderately five or more times per week for a duration of 30-minutes each time is sufficient for improvements in psychological well-being (Dimeo et al., 1999; Pinto and Trunzo, 2004). More gentle exercises, such as yoga, have also been found to be effective in terms of stress reduction (Rao et al., 2008) and improving mood (Vadiraja et al., 2009), with both studies introducing supervised yoga sessions during treatment as well as providing preparation for home-based yoga post-treatment. This again highlights the importance of exercise maintenance, with initial supervised exercise being a potentially useful first step towards self-initiated exercise.

- The importance of exercise for psychological well-being should be counselled to patients during and after cancer treatments and included in their multimodal information materials.
- Aerobic and resistance exercise should start during initial cancer therapies to prevent weight again and improve muscle strength.
- Supervised longer term aerobic and resistance exercise should be locally available for patients and their relatives in groups or individually.

Table 3: Summary of Evidence for Lifestyle and Psychological Well-Being

Authors	Design	Cohort	Intervention	Outcome
Dimeo et al. (1999)	RCT (n=59)	Breast Cancer; Lung Cancer; Non-Hodgkin's Lymphoma	30mins aerobic exercise during hospitalisation for high-dose chemotherapy	SS improvements in psychological distress.
Pinto and Trunzo (2004)	Cohort (n=79)	Breast Cancer	Self-reported regular exercisers	SS more positive attitudes and sexual attractiveness.
Courneya et al. (2007)	RCT (n=242)	Breast Cancer	Supervised aerobic and resistance training	SS improvements in self-esteem and psychological functioning.
Scheier et al. (2007)	RCT (n=252)	Breast Cancer	Education and nutritional counselling	SS impact on levels of depressive symptoms, mental and physical health, and optimism.
Rao et al. (2008)	RCT (n=68)	Breast Cancer	Yoga pre-surgery and during post-operative recuperation	SS decrease in anxiety and symptom severity. SS improvements in QoL.
Lengacher et al. (2009)	RCT (n=84)	Breast Cancer	6-week mindfulness-based stress reduction (MBSR)	SS lower levels of depression, anxiety, and fear over recurrence.
Vadiraja et al. (2009)	RCT (n=72)	Breast Cancer	6-week yoga and relaxation during adjuvant radiotherapy	SS improvement in emotional function and positive affect. SS decrease in negative affect.

- SS – Statistically significant.

Quality of Life

The advancements in diagnosis and treatment that have contributed to the rise in survivorship are a magnificent feat for medical science. However, it is important to recognise that this has also resulted in an increase in the number of people living with the physical and psychological consequences of cancer and its treatment. Quality of life outcomes are thus becoming just as important as 'hard' outcomes such as mortality (Rosenbaum, Fobair and Spiegel, 2006), An increase in evidence showing QoL to be more predictive of cancer survival than measures of performance status (Eton et al., 2003; Wenzel et al., 2005). Several factors effect Qol, including the physical and psychological disabilities caused by the cancer and its treatments as well as social depravation, family, cultural and financial support but a good QoL questionnaire should be able to encompass most of them to give a measurable score which can be statistically compared in clinical trials (Cella et al., 2009). This review addresses interventions which have been evaluated for their influence on QoL. In the main the published literature emphasises exercise including, aerobic, resistance, dance and Chinese movement either on their own or combined with nutrition counselling or Cognitive Behaviour Training.

Self-Reported Physical Activity

Lynch et al. (2008) examined physical activity and QoL data collected as part of the Colorectal Cancer and Quality of Life Study. Telephone interviews were conducted at approximately 6, 12, and 24 months after diagnosis 1,966 patients with colorectal cancer. They reported that participants 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).

Supervised Aerobic and Resistance Training

Courneya et al. (2003) evaluated QoL outcomes in relation to exercise in a RCT of breast cancer survivors who had completed surgery, radiotherapy or chemotherapy. Participants trained three times per week for 15-weeks on recumbent or upright cycle ergometers. Exercise duration began at 15-minutes for weeks 1-3, and then systematically increased by five-minutes every 3-weeks to 35-minutes for weeks 13-15. The exercise group completed 98.4% (44.3 of 45) of the prescribed exercise sessions, demonstrating high adherence rates. Overall QoL increased by 9.1 points in the exercise group compared with 0.3 points in the control group. Change in peak oxygen consumption correlated with change in overall QoL, demonstrating a relationship between exercise and increases in QoL.

Daley et al. (2007) conducted an RCT which provided further support for aerobics exercise and QoL in women who were not regularly active and who had been treated for localised breast cancer 12-36 months previously. The women were randomised to one of three groups:

exercise therapy – aerobics (n = 34); exercise-placebo – body conditioning (n = 36); or, usual care (n = 38). The primary outcome was differences in QoL at the 8-week follow-up (FACT-G). In the exercise therapy group, 50-minute one-to-one sessions took place with an exercise specialist three times per week for 8-weeks. Adherence to the interventions was good; 77% of the exercise therapy and 88.9% of the exercise-placebo groups, respectively, attended 70% (at least 17 of 24 sessions) or more of the sessions. The results demonstrated a significant mean difference of 9.8 units in QoL scores, favouring aerobic exercise therapy at 8-weeks compared to usual care.

Segal et al. (2003) reported an RCT comparing supervised resistance exercise versus control in 135 men with prostate cancer who were scheduled to receive androgen deprivation therapy for at least 3-months. The primary outcome was QoL measured by a prostate cancer–specific health-related QoL questionnaire (FACT-P). Secondary outcomes were muscular fitness and body composition measured by anthropometric data and scored questionnaire responses. Men in the intervention group met with a certified fitness consultant within 7-days of the pre-assessment. The fitness consultant provided patients with the results of their exercise assessment and introduced the personalised resistance exercise program. Each participant was led through a standardised series of warm-up and cool-down exercises to be performed at each exercise session. Resistance exercise consisted of nine strength-training exercises carried out under supervision three times per week, at 60% to 70% of one-repetition maximum (1-RM; the maximum amount of weight that can be lifted once), estimated from the standard load test. Two sets of 8-12 repetitions of the following nine exercises were performed: leg extension, calf raises, leg curl, chest press, latissimus pull down, overhead press, triceps extension, biceps curls, and modified curl-ups. Sixty percent of the participant's 1-RM was used as the starting resistance. Patients were instructed to increase the resistance by 5lb when they were able to complete more than twelve repetitions. Attendance at the prescribed resistance exercise sessions averaged 79% (28 of 36 sessions). During the intervention period, eight men (9.8%) dropped out in the intervention group compared with twelve men (16.4%) in the control group.

There was a significant improvement in QoL outcomes in the intervention group and a significant decline in the control group. Resistance exercise improved QoL regardless of whether men were treated with curative or palliative intent, or whether androgen deprivation therapy had been received for less than one-year or ≥1 year. The authors commented that another possible explanation for the difference in QoL outcomes might be that the men in the intervention group were also receiving structured attention three times per week, whilst the control group were not.

Milne et al. (2007) reported a RCT with women who had stage I–II breast cancer, evaluating the effects of a 12-week supervised aerobic and resistance exercise program. They were within 24-months of their cancer diagnosis. Participants were asked to attend the rehabilitation clinic three times a week for 12-weeks any time during clinic hours. The sessions, three times a week, were supervised by two exercise physiologists who ensured every participant received one-on-one contact during each session. The program included an

aerobic component that utilised the cycle and rowing ergometers, the mini-trampoline, and the step-up blocks. The cardiovascular component of the program was conducted for 20-minutes and ended with a five-minute cool down. The resistance training component consisted of twelve different exercises (chest press, chest extension, biceps curls, triceps extension, leg extension, leg curls, hip abduction and adduction, back extension, abdominal crunches, standing fly's and leg press). For each exercise, participants performed two sets of 10–15 repetitions of lightweights and progressed to a heavier weight once the current weight and repetitions could be achieved easily and with good form. Finally, five-minutes of stretching were performed at the beginning and end of each session in order to increase flexibility. The average attendance was 60.4%. The intervention demonstrated a significant increase in overall QoL from baseline to week six, 12, 18 and 24 weeks. Benefits were demonstrated across several subscales of the FACT-B questionnaire including physical well-being, emotional well-being, functional well-being and breast cancer concerns all demonstrated the same pattern of results.

Cadmus et al. (2009) report on two RCTs: The Increasing or Maintaining Physical Activity during Cancer Treatment (IMPACT) study and the Yale Exercise and Survivorship (YES) study. Both studies examine the impact of a 6-month moderate to vigorous sports and recreational physical activity versus usual care on QoL among breast cancer survivors (n = 45 and n = 67, respectively). The IMPACT study tested a home-based approach among newly diagnosed survivors, while the YES study examined a combined supervised – and hone-based intervention for post-treatment survivors. Both studies are reported together in order to compare the effects of exercise at two different points in survivorship. Data collection for both studies involved a screening phone call, baseline interview and clinic visit, and 6-month follow-up. QoL was assessed using the FACT-B and SF-36.

Both exercise interventions were based on the national recommendation of 30-minutes of moderate to vigorous physical activity five days per week. Participants chose from a variety of sports and recreational activities, with most women performing walking as their main activity. The IMPACT home-based exercise programme was based on the theory of planned behaviour and transtheoretical model, and was thus designed to promote self-efficacy and help participants overcome common barriers to exercise. At the beginning of the programme, each participant received an educational book, a binder containing specialised weekly informational handouts, and a Polar heart rate monitor (used to maintain activity at 60-80% of predicted maximal heart rate). Participants recorded each session in a 7-Day Physical Activity Log and returned these logs once every month. Each participant was taught exercise techniques and principles during weekly phone-based meetings with a staff member, calls lasting approximately 20-minutes and including discussion of the previous week and goal-setting for the next week.

The YES intervention comprised a supervised training programme at a local health club, where participants exercised during designated session three days a week. They also exercised an additional two days per week at the health club or on their own.

Exercise was not associated with QoL benefits in the full sample of either study; however, exercise was associated with significantly improved social functioning among post-treatment survivors who reported low social functioning at baseline (Cadmus et al., 2009).

Dance and Movement

Sandel et al. (2005) report on a cross-over RCT testing the outcomes of a 12-week dance and movement exercise programme in 38 women within 5-years of treatment for breast cancer. The study included a waiting list control (n = 19) and crossover at 13-weeks. Women attended two supervised dance sessions for six weeks and one session per week for an additional 6-weeks, for a total of eighteen sessions. All outcome measures were obtained at baseline, 13-weeks, and 26-weeks, and included the FACT-B as the primary outcome as well as the SF-36 as a secondary measure of general QoL and the Body Image Scale. At week 14, the waiting list group crossed over and performed the movement program during weeks 14-25, whereas the intervention group continued their usual activities.

The classes followed a standardised regime: Warm-up (10-15 minutes) - Every session began with breathing and stretching designed to improve lymphatic drainage. This included deep breathing, head and neck stretches, shoulder rotations, torso contractions, side-to-side arm extensions, body torso lengthening, and large arm circles. This was usually done sitting in a circle, to percussion music orchestrated for these movements. Bilateral stretching exercises in a standing position followed, using a chair for support. During the first few weeks, lower body movements alternated with upper body movements; Core Exercises - Upper extremity movements of the shoulder, elbow, and wrist were performed bilaterally to music, with four or fewer repetitions per side. Imagery was used to encourage a progressive increase in the ROM in shoulder abduction, forward and backward flexion, and adduction (e.g., “reaching for the stars,” “lifting a tray of fruit”). Lower body movements, such as side-to-side hip swings, walking around with various attitudes, and balance exercises with chairs, were inserted to provide rest from upper body exertion and to increase energy flow. Exercises using resistance bands were introduced in the fifth week; Dance Movements (25-30 minutes) - The dance components were designed to address, in a subtle way, the existential challenges that most women report following the diagnosis and treatment of breast cancer: body image, sexuality, sense of control, meaning in life, grief, and loss. Movements were simple and designed for women with no dance experience, and who may have poor balance or no confidence. Initially, four simple movements were taught to music and repeated several times as a “routine.” As the women learned a repertoire of familiar dance moves (by the fifth week), they were able to follow the instructor’s lead in a more spontaneous flowing dance. The dances used a variety of musical traditions including Celtic, American, Jazz, Afro-Cuban, Reggae, Middle-Eastern, and Cajun. Rhythmic patterns based on multiples of four beats were most adaptable to the tempo of the movements; a waltz rhythm in multiples of three beats was also successful. No fast movements were performed although fast music was used. A large, tubular stretch band made of blue jersey was introduced into the group dance to provide an external focus and decrease anxiety (i.e., something to hang onto). As each

cohort progressed, they became less reliant on such props and more comfortable with moving their bodies. There was also a 10-minute 'wrap-up' at the end of each session with a seated ritual using gentle stretching, meditative movements, and quiet music. Finger rolls and extensions were performed. The final activity was focused breathing with soothing music, mirroring the beginning of the session. As the music ended, the leader asked the group how they were feeling and whether there were any questions, allowing for a 10-30 minutes exchange of information.

A total of 35 (92%) women completed the regimen. Reasons for dropping out included fatigue, other commitments, and one participant reported shoulder discomfort. No falls or acute injuries occurred during the dance sessions.

Breast cancer–specific QoL (FACT-B) improved significantly in the intervention group compared to the waiting list group at 13-weeks, which remained unchanged.

Chinese Exercises

Mustian, Palesh, and Fleckstein (2008) reported a pilot RCT comparing QoL and functional capacity in 21 breast cancer survivors provided with Tai Chi Chuan (TCC; a moderate intensity Chinese exercise) versus psychosocial support. The exercise intervention lasted for 12-weeks (60-minutes three times a week). The TCC group demonstrated significant improvements in functional capacity, including aerobic capacity, muscular strength, and flexibility, as well as QoL; the psychosocial support therapy group showed significant improvements only in flexibility, with declines in aerobic capacity, muscular strength, and QoL.

Oh et al. (2009) reported a RCT examining the QoL outcomes of Medical Qigong (MQ), a mind–body practice that uses physical activity and meditation to harmonise the body, mind and spirit. 162 patients with a confirmed diagnosis of malignancy of any stage and an expected survival length of >12-months were randomised to control or to 10-weeks with two supervised 90-minute sessions per week. Each session consisted of 15-minutes discussion of health issues, 30-minutes gentle stretching and body movement in standing postures, 15-minutes movement in seated posture, 30-minutes meditation including breathing exercises and visualisation. Drop-out was relatively high (although equivalent between the groups) - 32% in the intervention arm and 35% in the control.

At 10-week follow-up, participants in the MQ group reported larger improvements in QoL (FACT-G), than those in the usual care group. QoL sub-domain analyses also showed that changes in scores were significantly larger for all sub-domains of QoL (physical, functional, emotional, and social well-being) in the intervention compared with the control group.

Exercise combined with Nutritional Counselling

Mosher et al. (2009) reported at a prospective cohort study examining the diet and exercise patterns of 753 breast, prostate, and colorectal cancer survivors who were at least 5-years post-diagnosis, seeking to identify any relationships with QoL outcomes. Survivors underwent two 45-60 minute telephone surveys administered by the Diet Assessment Center. The length of time between interviews ranged from 2-days to 3-weeks. Other measures completed before the intervention include: physical activity (The Community Healthy Activities Models Program); dietary intake (assessed from two unannounced, 24-hour recalls performed by trained interviewers before diet quality was assessed via the Healthy Eating Index 05 (HEI05); BMI and, QoL (SF-36).

The data demonstrated that greater weekly minutes of exercise were associated with better physical QoL, including less pain and better health perceptions, physical functioning, and vitality. More exercise was also correlated with better social functioning. Diet quality had a positive association with a range of physical QoL outcomes in analyses that were adjusted for age, level of education, and co-morbidities. Greater BMI was associated with worse physical QoL, including greater pain and role limitations because of physical problems and worse health perceptions, physical functioning, and vitality. These associations remained significant when adjusting for age, ethnicity, level of education, cancer-type, and co-morbidities. However, a limitation to this study is the questionable reliability of self-report data.

Exercise combined with Cognitive Behavioural Training

Korstjens et al. (2008) reported a RCT comparing physical training (PT) with combined physical and cognitive behavioural training (PT+CBT) and also with controls on a waiting list. A mixed sample of 209 cancer survivors had completed curative cancer treatment at least 3-months previously. But were judged by a medical specialist to have at least three of the following criteria: physical complaints, reduced physical capacity, psychological problems, increased fatigue, sleep disturbances, and problems in coping with reduced physical and psychosocial functioning due to cancer.

Each exercise session consisted of individual aerobic bicycle training (0.5 hour), based on baseline graded exercise testing, muscle strength training (0.5 hour), and group sports and games (1-hour). Sports and games, such as badminton, soccer, swimming, and balancing games, were aimed at promoting enjoyment in sports and improving self-efficacy to incorporate sporting activities into daily life and to adopt a physically active lifestyle. Additionally, patients received information on exercise physiology, illness perceptions, and self-management to support them in regulating their PT. Participants learned to use by themselves heart rate sport testers, the Borg Scale for dyspnoea and fatigue, and training logs to monitor and evaluate their performance; they received feedback, information, and support

from their therapists in regulating their performance. During the first 4-weeks, participants followed a tailor-made basic training program based on individual baseline testing. Then, in cooperation with the therapists, participants determined their personal goals for training from week five onward. They could choose one of four modules: improvement of physical condition; improvement of muscular strength; coping with fatigue; or, handling limitations.

CBT included interactive psycho-education and structured self-management skills training. This training was formatted in line with a cognitive behavioural problem-solving therapy protocol for individual cancer patients and a group problem-solving protocol successfully applied in patients with non-specific low back pain. CBT aimed to enable participants to effectively solve their personal problems associated with cancer. They learned to apply self-management skills in striving for personal goals (e.g., in work, household, hobbies, physical activity, family relationships, and social contacts). Generalisation to daily life during and after rehabilitation was promoted by practicing activities during sessions and by homework assignments (maximum of 0.5 hour weekly). Every session was structured: 1) summarising the previous week's session and exchanging daily life experiences; 2) discussing home assignments; 3) introducing new topics or self-management skills; 4) practicing self-management skills; 5) introducing the next homework assignments; and 6) relaxation exercises. Participants used a workbook containing a summary of the training, self-management worksheets and assignments as well as information on additional topics relevant to cancer patients. The first 3-weeks focused primarily on exchanging participants' experiences with cancer, psycho-education about stress, relaxation, fatigue, exercise physiology, illness perceptions, and promoting optimism and self-efficacy for self-management. From week four onward, participants were primarily trained in applying self-management skills to realize personal goals by practicing the following steps in the circular problem-solving process: 1) problem orientation; 2) problem definition and formulation, and goal setting; 3) generation of alternative solutions; 4) decision-making; and 5) solution implementation and verification.

Compared with no intervention, participants in both rehabilitation groups showed significant and clinically relevant improvements in role limitations due to physical problems, and in physical functioning, vitality, health change and QoL (SF-36), measured at baseline 3 and 6 months. Adding cognitive-behavioural training to group-based self-management physical training did not have additional beneficial effects on cancer survivors'

Conclusion and Recommendations **(Lifestyle, Exercise and QoL)**

There is convincing evidence that exercise and lifestyle interventions can improve the QoL of cancer survivors. This benefit has been proven through well conducted randomised trials addressing interventions during active treatments and in the long-term survivorship stage.

Lifestyle interventions appear to help people with a wide range of cancer types who have received treatments ranging from surgery, chemotherapy, radiotherapy or hormonal therapies,

although no trials have yet been published specifically addressing the newer biological therapies. Even when not directly associated with overall QoL, exercise has been found to significantly improve social functioning among post-treatment survivors (Cadmus et al., 2009). The benefits of physical activity on holistic QoL appear to be present under a number of conditions, be the physical activity supervised or home-based (Cadmus et al., 2009), individualised or group-based (Korstjens et al., 2008). A vast array of different types of exercise techniques have been tested in the studies evaluated in this review, highlighting the potential for survivors to choose activities according to preference. Considering the evidence for lifestyle and QoL, the following recommendations would likely benefit patients:

- Counsel patients on the benefits of exercise to help reduce the psychological morbidity associated with cancer and its treatments.
- Provide information materials on the benefits of exercise to help reduce the psychological morbidity associated with cancer and its treatments.
- Consider hospital-based exercise programmes for patients early in their cancer treatment pathway.
- Provide practical information on local existing group and individual exercise facilities for long-term rehabilitation.
- Liaise with local exercise establishments to provide long-term exercise programmes by suitably trained exercise professionals.

Table 4: Summary of Evidence for Exercise and QoL

Authors	Design	Cohort	Intervention	Outcome
Courneya et al. (2003)	RCT (n=53)	Colorectal Cancer	15-weeks supervised aerobic and resistance training	Increased QoL.
Segal et al. (2003)	RCT (n=135)	Prostate Cancer	Supervised resistance exercise	SS improvement in QoL.
Sandel et al. (2005)	RCT (n=38)	Breast Cancer	12-weeks dance and movement programme	SS improvement in QoL.
Daley et al. (2007)	RCT (n=117)	Breast Cancer	8-weeks, 50mins supervised aerobic and resistance training	SS improvement in QoL.
Milne et al. (2007)	RCT (n=60)	Breast Cancer	12-weeks supervised aerobic and resistance training	SS increase in QoL.
Korstjens et al. (2008)	RCT (n=209)	All Cancers	Exercise combined with CBT	SS better physical functioning, vitality, and QoL.
Lynch et al. (2008)	Cohort Study (n=1,966)	Colorectal Cancer	Self-reported physical activity of at least 150-minutes per week	Higher QoL.
Mustian, Palesh, and Flecksteiner (2008)	RCT (n=21)	Breast Cancer	12-weeks, 60mins three times per weeks Tai Chi Chaun	SS improvements in functional capacity, muscular strength, flexibility, and QoL.
Cadmus et al. (2009)	Two RCTs: IMPACT (n=45); YES (n=67)	Breast Cancer	6-months, 30mins per day sports and recreational physical activity	Not associated with QoL benefits. SS improvement in social functioning.
Mosher et al. (2009)	Prospective Cohort Study (n=753)	Breast Cancer; Prostate Cancer; Colorectal Cancer	Self-reported diet and physical activity	Exercise SS associated with better QoL. > BMI with worse QoL.
Oh et al. (2009)	RCT (n=162)	Range of cancers; mainly Breast and Colorectal.	10-weeks Medical Qigong	SS larger improvements in QoL.
Vadiraja et al. (2009)	RCT (n=72)	Breast Cancer	6-week yoga and relaxation during adjuvant Rxt	SS improvement in emotional function and positive affect.

- SS – Statistically significant. BMI – Body Mass Index; IMPACT - Increasing or Maintaining Physical Activity during Cancer Treatment study; YES – the Yale Exercise and Survivorship study; CBT – cognitive behavioural training.

Lymphoedema

The presence of cancer in the lymph nodes of the axilla is the most important prognostic factor in breast cancer, and thus the removal and evaluation of these lymph nodes are integral components of breast cancer management (Morrell et al., 2005). However, removal of the lymph nodes can result in a number of side-effects, including lymphoedema (Swenson et al., 2001). The more lymph nodes that are removed, the higher the risk of developing the condition, which is estimated to affect about 30% of women after breast cancer treatment (Deo et al., 2004; Williams et al., 2005). It manifests usually as a swelling to the affected arm, but can also occur in the hand, trunk and breast. It can develop immediately or many years after treatment (Mortimer et al., 1996). Whenever it develops, lymphoedema is a chronic, debilitating condition that can cause severe physical and psychological morbidity as well as a reduction in quality of life (Deo et al., 2004).

This review summarises studies which evaluated intervention lifestyle strategies including aerobic exercise, weight lifting and diet in addition to the standard management of physiotherapy and compression bandaging (Moseley and Piller 2008, de Rezende et al., 2006, Deo et al., 2004).

Physiotherapy

De Rezende et al., (2006) reported a prospective RCT testing the efficacy of two types of physiotherapy on shoulder function and lymphatic disturbance in post-operative rehabilitation, as performed with 60 breast cancer patients who had undergone modified radical mastectomy or quadrantectomy with axillary dissection. Participants were randomised to either the directed physiotherapy group or the free-moving physiotherapy group. The physiotherapy technique used in was kinesiotherapy, based on spontaneous exercises including movements for flexion, extension, abduction, adduction and internal and external rotation of the shoulder, either isolated or combined. The directed group performed physiotherapy with a regimen of nineteen exercises, all of the movements being performed ten times with a 60-second interval between exercises. The free group performed the exercises without a previously defined sequence or number of repetitions, the exercises being done to the rhythm of music. Three exercises were started the first day after surgery in both groups. All patients were advised to maintain free activity with the compromised limb in their daily activities. Starting 48-hours after surgery, the exercises were performed in 40-minute sessions with a frequency of three times a week for a period of 42-days. The exercises were practiced in groups of 5-20 women and administered by a team of five physical therapists and ten physical therapy trainees. Results indicated that the averages of the flexion, abduction and external rotational movements of the shoulder showed significantly better recovery in the directed group compared to the free group, with there being no significant difference between the groups in terms of lymphatic disturbance.

Weight Reduction Dietary Interventions

Shaw, Mortimer, and Judd, (2007) examined the impact of diet and weight loss on lymphoedema in a UK RCT comprising two dietary intervention groups (a low-fat diet and a weight reduction diet) and a control group continuing their usual diet. Women with arm lymphoedema (n = 21) after treatment for breast cancer were recruited from the lymphoedema clinic at the Royal Marsden Hospital. The inclusion criteria was that the subjects had a swollen arm of 20% or greater excess volume when compared with the unaffected arm, and were in remission from cancer having had no chemotherapy or radiotherapy in the previous 12-months. After the 24-week period of dietary intervention there were significant differences in the mean body weight, BMI, skinfold thickness, and percentage body fat between the control group and both the weight-reduction and low-fat groups. There was a reduction in excess arm volume over the 24-week period but there was no significant difference between the three groups. However, there was a significant correlation between weight loss and a reduction in excess arm volume irrespective of the dietary group. There were small changes in arm volume of the unaffected arm over the 24-week period compared with changes in the arm affected by lymphoedema. There was a significant difference in mean weight loss between the three groups at both 12-weeks and 24-weeks. Weight loss occurred in all groups, with nine participants (60%) losing weight in the control group, eighteen (95%) in the weight-reduction group, and thirteen (76%) in the low-fat diet group. Overall, the study showed a slightly greater reduction in excess arm volume in both dietary intervention groups compared with the control, although this was not statistically significant. Post-hoc analysis demonstrated a statistically significant correlation between weight loss and loss of swollen arm volume irrespective of the reason for weight loss.

Moseley and Piller (2008) reviewed eleven studies for evidence supporting the benefits of a variety of exercise interventions for those with limb lymphoedema, using the findings to propose how exercise might be incorporated into self-management programmes. Their key findings were that exercise improved lymph clearance; reduce limb volume and improved subjective symptoms and is a viable option for people with lymphoedema.

Aerobic Exercise (ergonometry, rowing, movement)

Havas et al. (2000) found that two hours of steady exercise increased lymph clearance rate five-fold in the first 15-minutes, while the rest of the time it was increased 2–3 fold. These findings are confirmed by a study by Lane et al. (2005), which demonstrated increased lymphatic clearance in the hands of healthy women who performed arm crank ergonometry for five-minutes.

Moseley and Piller (2008) reviewed the safety of weight lifting among ladies with lymphoedema and concluded that a wide variety of strenuous exercise can be undertaken by those at risk of developing lymphoedema and those who already have the condition without adverse effects. Two studies have shown that women who have undergone breast cancer

treatment can participate in vigorous exercise, such as rowing and upper body exercise, without exacerbating the lymphoedema, and without increasing risk of lymphoedema in those women without the condition (Harris and Niesen-Vertommen, 2000; Lane et al., 2005). The ability to undertake more active exercise has also been demonstrated in other studies, including women with secondary arm lymphoedema undertaking resistive arm exercise with hand weights (McKenzie and Kalda, 2003; Johansson et al, 2004), a dance programme (Sandel et al., 2005) and a moderately intensive exercise programme which included aerobic and resistive exercise (Turner et al, 2004).

Exercise combined with Compression Garments

McKenzie and Kalda (2003) and Johansson et al. (2004), in two studies, examined the outcomes of exercising while wearing a compression garment (both of which involved resistive weight exercises. Both studies demonstrated a reduction in arm volume of 15ml (at 24-hours) and 2%, respectively. Interestingly, Johansson et al. (2004) also investigated the same resistive weight exercises without using a compression garment, which also produced the same reduction.

Supervised Aerobics and Resistance Exercise

Moseley et al. (2005) evaluated a programme of arm exercise combined with deep breathing. McKenzie and Kalda, (2003), Johansson et al., (2004), and Buckley et al. (2004) investigated resistive arm exercise with weights and a 30-minute limb aerobic exercise programme. Three of the studies that included control groups (McKenzie and Kalda, 2003; Box et al., 2004; Moseley et al., 2005) demonstrated either a minimal decrease in limb volume or an actual increase when compared with the exercise group. Of particular note is that two studies (Buckley et al., 2004; Johansson et al., 2004) demonstrated an average initial increase in arm volume (12ml in both studies), which was shown to be only a temporary increase in volume, with an overall volume decrease 20-minutes (24ml) (Buckley et al, 2004) and 24-hours (15ml) (Johansson et al., 2004) after exercise.

Hildegard, and Turner (2009) reported a RCT which assessed the implications of exercise in 32 women who completed breast cancer treatment at least 6-months prior and had subsequently developed unilateral, upper-limb lymphoedema. The intervention group participated in twenty supervised, group, aerobic and resistance exercise sessions over 12-weeks, whereas the control group was instructed to continue habitual activities. Average attendance was more than 70% of supervised sessions and there were no withdrawals. Mean ratio and volume measures at baseline were similar between the two groups although exercise did not exacerbate secondary lymphoedema.

Supervised Weight Training with Stretching

Ahmed et al. (2006) conducted a 6-month randomised controlled weight training trial to examine the incidence and symptoms of lymphoedema in 45 breast cancer survivors. Participants were 4-36 months post-treatment, and had axillary dissection as part of their treatment. Thirteen women had prevalent lymphoedema at baseline. The weight training intervention comprised a one-hour process: for the first 3-months of weight training, participants met twice-a-week with a certified fitness professional; performed warm-up, weight training, cool down, and stretching exercises. Nine common weight training exercises were performed using variable resistance machines and free weights, targeting muscles of the arms, back, chest, buttocks, and legs. For the upper body, participants started with no weight or half-pound wrist weights for each exercise. Women were also taught stretching exercises to increase range of motion. Participants were encouraged to continue lymphoedema self-care therapy during the study, and adherence to this was monitored at measurement visits. All but one intervention-group participant attended at least 80% of exercise sessions, and adherence did not vary by baseline lymphoedema prevalence, suggesting intervention acceptability. From baseline to 6-months, neither the incidence of lymphoedema nor the onset of lymphoedema symptoms varied in the intervention-group versus control-group participants.

Schmitz et al. (2009) published, in the New England Journal of Medicine, the largest and best designed RCT evaluating the influence of weight lifting on the incidence of lymphoedema and its consequences. One hundred and forty one women with breast cancer were randomised to a supervised weight lifting programme or control. They all had received an axillary node clearance and had completed adjuvant chemotherapy or radiotherapy. Both groups received standard lymphoedema advice. The intervention group received twice weekly supervised exercise sessions for 6 months. Weight lifting started with a warm up and warm down which included significant stretching exercises. The initial weight and escalation determined at each session by a certified exercise professional. At six months there was no statistical significance in arm thickness but muscle strength was improved and there was a significant difference in the number lymphoedema flares which required acute intervention (either infection or sudden deterioration in upper limb circumference.

Exercise for Leg Lymphoedema

Moseley et al. (2003) and Buckley et al. (2004) investigated the effect of exercise on secondary leg lymphoedema. These two studies demonstrated that both mechanical limb elevation plus passive exercise (Moseley et al., 2003) and 30-minutes of limb exercise (Buckley et al., 2004) can produce a reduction in limb volume and subjective improvements in symptoms. In the study by Moseley et al. (2003), the limb volume reduction was significant (330ml), while in Buckley et al.'s (2004) study it was much smaller (55ml). Both studies also demonstrated a volume reduction at follow-up, including at 20-minutes post-exercise (31ml) (Buckley et al., 2004) and one-month after trial completion (220ml) (Moseley et al., 2003).

Conclusion and Recommendations **(Lifestyle, Exercise and Lymphoedema)**

These results indicate a need to re-evaluate the common clinical guidelines that breast cancer survivors avoid upper body resistance activity for fear of increasing risk of lymphoedema. They all show that a wide range of exercises including vigorous aerobics and strenuous weight lifting are safe and supervised programmes are enthusiastically attended patients. No trial showed that exercise increased the severity of lymphoedema if already established or increased the incidence after axillary no clearance. A number of prospective studies reviewed by Moseley and Piller (2008) demonstrate that exercise can improve lymph clearance, reduce limb volume, and improve subjective symptoms and QoL. Furthermore, weight reduction, if initially overweight, improved limb circumference in those already suffering form lymphoedema. The most convincing RCT also showed a significant reduction in acute chronic lymphoedema flare events which are very distressing for those already suffering the inconvenience and indignity of lymphoedema. In addition to standard advice for treating and preventing lymphoedema, including the benefits of weight reduction and compression garments the following recommendations are appropriate based on the published evidence:

- Medical education: Clinical members of the multidisciplinary breast cancer team staff require education to ensure they give appropriate verbal advice to patients.

- Patient information: the benefits of exercise to prevent and treat lymphoedema should be included in written and electronic patient information materials.

- A supervised exercise programme including weight lifting on the affected arm should be available for patients.

Table 5: Summary of Evidence for the Benefits of Exercise and Lifestyle on Lymphoedema

Authors	Design	Cohort	Intervention	Outcome
Havas et al. (2000)	RCT (n=8)	Endurance-trained men	2-hours of steady exercise.	Increased lymph clearance rate five-fold in first 15mins and 2-3 fold rest of time.
McKenzie and Kalda (2003)	RCT (n=14)	Breast Cancer	Resistive weights exercise combined with compression garments	Reduction in arm volume of 15ml.
Johansson et al. (2005)	RCT (n=31)	Breast Cancer	Exercise combined with compression garments	Reduction in arm volume of 2%
Moseley et al. (2005)	RCT (n=38)	Breast Cancer	Arm exercises combined with deep breathing	Reduced limb volume.
Ahmed et al. (2006)	RCT (n=45)	Breast Cancer	6-months, twice weekly supervised weight training	At minimum, exercise does not exacerbate lymphoedema.
de Rezende et al. (2006)	RCT (n=60)	Breast Cancer	Supervised kinesiotherapy (physiotherapy)	SS better recovery.
Shaw, Mortimer, and Judd (2007)	RCT (n=21)	Breast Cancer	24-week dietary intervention	Reduction in arm volume. Correlation between weight loss and arm volume.
Moseley and Piller (2008)	Systematic Review (n=11)	Breast Cancer	A variety of exercise interventions.	Improved lymph clearance and symptoms. Reduced limb volume.
Hayes, Hildegard, and Turner (2009)	RCT (n=32)	Breast Cancer	12-weeks supervised aerobic and resistance training	Exercise did not exacerbate lymphoedema.

SS – Statistically significant.

Bone Health (Osteoporosis)

Osteoporosis is a condition in which the bones become less dense and more likely to fracture, which in turn can result in significant pain and disability. If undetected, bone loss can progress for many years without symptoms until a fracture occurs. Pre-menopausal women who have had breast cancer treatment may be 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 whilst men who receive hormone deprivation therapy for prostate cancer also have an increased risk of developing osteoporosis (National Institutes of Health Osteoporosis and Related Bone Diseases, 2009). Among post menopausal women, it has been reported that 80% of breast-cancer patients have osteopenia (below normal bone-mineral density [BMD]) or osteoporosis at initial diagnosis (Twiss et al., 2001). Osteopenia, osteoporosis, and increased rates of fracture have been noted in survivors of many cancers, including breast, prostate, testicular, thyroid, gastric, and CNS cancers, as well as non-Hodgkin's lymphoma and various haematological malignant diseases (Brown et al., 2003);

Other 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 and Joy, 2005).

This section reviewed the evidence that lifestyle factors may influence the prevention, development, progression or severity of impairments of bone mineral density among cancer survivors. It categorised self-management lifestyle strategies into exercise including home-based aerobics, walking and resistance programmes, diet including plant proteins, Soya product and fibres, and other lifestyle factors including excessive alcohol intake and smoking.

Home-Based Aerobics and Resistance Programmes

Schwartz, Winters-Stone, and Gallucci, (2007) evaluated the impact of aerobics and resistance training on BMD in an RCT involving 66 women with histologically confirmed invasive stage I-III breast cancer. Strenuous regular exercisers, defined as women who exercised more than 250-minutes per week were excluded. At baseline (before chemotherapy) and at six-months, bone mineral density, aerobic capacity (12-minute walk), and upper and lower body muscle strength (single-repetition maximum test) were measured. Women were randomised to one of three groups: home-based aerobic exercise; home-based resistance exercise; or usual care, and stratified according to menopausal status (pre-menopausal or post-menopausal). Post-menopausal women were defined as those who had cessation of menses for at least six consecutive months prior to beginning chemotherapy.

Women randomised to the home-based aerobic exercise intervention were instructed to choose an aerobic activity they enjoyed (e.g. walking, jogging) and exercise for 15-30

minutes four days per week for the duration of the study, at a symptom-limited, moderate intensity such that they were breathing hard but able to talk.. Caloric expenditure during each exercise session was measured using Caltrac Accelerometers™. Resistance exercise subjects were instructed to exercise at home four days per week using resistance bands and tubing. The average decline in BMD was -6.23% for usual care, -4.92% for resistance exercise, and -0.76% for aerobic exercise. Pre-menopausal women demonstrated significantly greater declines in BMD than post-menopausal women. Aerobic capacity increased by almost 25% for women in the aerobic exercise group and 4% for resistance exercise. Participants in the usual care group showed a 10% decline in aerobic capacity. The data suggest that weight-bearing aerobic exercise attenuates declines in BMD and that aerobic and resistance exercise improve aerobic capacity and muscle strength at a time when women generally show marked declines in functional ability.

Waltman et al. (2009) evaluated the efficacy of a strength and weight training programme in 223 post-menopausal women who had completed breast cancer treatment (except tamoxifen and aromatase inhibitors) at least 6-months earlier. The women were randomised to the two treatment groups: exercise with medication ($n = 110$) and medication only ($n = 113$). The medication taken by both groups included: risedronate (osteoporosis medication), calcium (1500mg per day) 400 IU vitamin D per day, and vitamin D (400 IU per day). Participants who were 50% or greater adherent to exercises were significantly less likely than participants on medications alone, to lose BMD at the total hip and femoral neck.

Diet, Plant Proteins and Fibres

Weikert et al., (2005) performed a sub-analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) Potsdam cohort study which included 8,178 females and examined the association between protein intake, dietary calcium, and bone structure. It was concluded that high consumptions of animal protein may be unfavourable, whereas higher vegetable protein may be beneficial to bone health. These results support the hypothesis that high calcium intakes combined with adequate protein intake based on a high ratio of vegetables to animal protein may be protective against osteoporosis. Indeed, evidence has demonstrated the relationship between lower incidence of osteoporosis in Asian women and vegetarian populations due to a diet rich in vegetables and fruit (Fujii et al., 2009; Merill and Aldana, 2009; Thorpe et al., 2008). Furthermore, a large-scale dietary modification intervention of post-menopausal women (n = 48,83) showed that an increased consumption of plant proteins and fibres from fruits, vegetables and grains reduced the risk of multiple falls and slightly lowered hip BMD, although it did not change the risk of osteoporotic fractures (McTiernan et al., 2009).

New et al. (2003; 2004) further highlighted the benefits of plant proteins and fibres on bone health in two reviews by where a positive link between a high consumption of fruit and vegetables and bone health has been demonstrated. In the first report, it was found that fruit

and vegetables have beneficial effects on bone mass and bone metabolism in men and women across the age ranges, whilst in the second review it was concluded that although the impact of a vegetarian diet on bone health is much more complex than merely being related to diet, vegetarians do tend to have 'normal' bone mass.

Soya Products

Marini et al., (2008) reported a randomised, double-blind, placebo-controlled trial of the soya derivative genistein aglycone and its effects on bone health after 3-years of 389 women with breast and endometrial. Bone mineral density increases were greater with genistein for both femoral neck and lumbar spine compared to placebo. There were no differences in discomfort or adverse events between groups, the conclusion being that after 3-years of treatment, genistein exhibited a promising safety profile with positive effects on bone formation in this cohort of osteopenic, post-menopausal women

Ryan et al. (2007) present some findings on osteoporosis risk, as elicited from the US05 study, a randomised, placebo-controlled study of zoledronic acid versus placebo in patients with prostate cancer (n = 120) without bone metastases and within the first 12-months of ADT. Participants completed a baseline questionnaire regarding osteoporosis risk factors, eliciting the following medical and lifestyle information. The accumulated data demonstrated that osteopenia or osteoporosis was detected in two thirds of the men. A positive association between BMI and bone density of the hip was observed, suggesting that a higher BMI is protective of bone density loss in men with prostate cancer and that weight loss could increase risk of osteoporosis. Calcium and vitamin D supplement use by study subjects was associated with greater bone density measurements at the total hip, supporting the use of dietary supplementation in patients with prostate cancer. Greater bone density was found in men consuming seven or more alcoholic beverages weekly than in non-drinkers, highlighting the potential benefits of moderate alcohol consumption, as also demonstrated by the National Osteoporosis Risk Assessment longitudinal observational study (Siris et al., 2001).

Ryan et al. (2007) evaluated the importance of weight in relation to BMD amoung breast cancer survivors. They found that smoking and being underweight (BMI less than 18.5) were associated with lower BMD.

Conclusion and Recommendations (Bone Health)

The evidence summarised within this review suggests that lifestyle factors, although not increasing bone density, have a significant impact on maintaining BMD and avoiding fractures. The evidence for benefits of lifestyle have been reported mainly for survivors of breast and prostate cancer but as impairments of bone health effects patients with a wide variety of cancer types it is likely to be treatment and person specific rather cancer specific. The benefits applied to those embarking on lifestyle programmes alone or in conjunction with vitamin D and calcium supplement or bisphosphonates. Based on this evidence the benefits

of exercise and lifestyle factors to prevent osteoporosis and maintain bone health should be emphasised to patients verbally and within in multimodal information materials.

Patient information:

- Stop smoking
- Avoid excess alcohol intake
- Incorporate more physical exercise within the activities of daily living
- Perform regular aerobic and resistance exercise in formal programmes
- Eat a diet rich in vegetables, pulses, fruit and grains
- Increase intake of Soya based foods (beans, miso, tempeh, soy milk, tofu)
- Ensure adequate calcium intake (nuts, dairy products, shell fish)
- Ensure regular gentle sun exposure to increase Vitamin D levels
- Avoid being underweight (BMI < 19)

Medical interventions:

- Ensure information pathways include the benefits of lifestyle on bone health
- Provide detailed information on local exercise classes including walking groups, gyms, dance and aerobics classes
- Provide local exercise rehabilitation classes or supervised facilities
- Measure bone density after cancer treatment
- Advise supplements or bisphosphonates according to national guidelines.

Table 6: Summary of Evidence for Lifestyle and Bone Health

Authors	Design	Cohort	Intervention	Outcome
Weikert et al. (2005)	Cohort (n=8,178)	Breast Cancer	Self-reported dietary patterns	Vegetables (plant proteins and fibres) are beneficial for bone health.
Ryan et al. (2007)	RCT (n=120)	Prostate Cancer	Self-reported lifestyle patterns	A positive association between BMI, Ca and vitamin D supplement and BMD of the hip.
Schwartz, Winters-Stone, and Gallucci (2007).	RCT (n=66)	Breast Cancer	Aerobic and resistance exercise	Improved aerobic capacity and muscle strength.
Marini et al. (2008)	RCT sub-cohort (n=138)	Breast Cancer; Endometrial Cancer	Genistein aglycone daily, plus calcium and vitamin D	Positive effects BMD.
Swenson et al. (2009)	RCT (n=62)	Breast Cancer	Prescribed physical activity during chemotherapy, plus oral calcium and vitamin D	Less effective in preventing bone loss.
Waltman et al. (2009).	RCT (n=223)	Breast Cancer	Strength and weight training, plus risedronate, calcium and vitamin D	At a minimum, BMD was maintained.

SS – Statistically significant; BMD – Bone mineral density.

Overall Conclusions, Discussion and Recommendations

A number of methodological limitations confound the interpretation of the benefits of exercise and diet after a diagnosis of cancer from other risks such as smoking, body size, supplements and analgesic intake. Furthermore, many of the studies are of a small sample size, lack long-term follow-up. Nevertheless, despite these caveats there is now persuasive evidence that a healthy lifestyle during and after cancer is associated with improved physical and psychological well-being, reduced risks of treatment, enhanced self-esteem, reduced risk of recurrence, and improved survival. Prising the individual anti-cancer components of a healthy lifestyle will require extensive further evaluation and even then they are likely to be multi-factorial.

In terms of slowing progression of an existing cancer the only prospective data comes from men with prostate can where, in some on active surveillance, the slow progression allows time for alternative interventions (Thomas et al., 2006). Although these trials are relatively small, they suggest a useful role for dietary and exercise advice for men with prostate cancer as a complement to active surveillance. This includes more fruit, vegetables, particularly those containing high levels of antioxidants including pomegranates and tomatoes. The data on taking extra dietary supplements is conflicting and requires further research particularly lycopene and Soya products.

In terms of reducing the risks of relapse, evidence is strongest following breast, bowel, lung, head and neck cancers but self help lifestyle strategies are likely to be person specific rather than disease or treatment specific so are likely to apply to all patients recovering from cancer. The main areas of evidence are categorised as:

Exercise:

- Include more physical options as part of the activities for daily living (Appendix 1)
- Aim to regularly participate in at least 2.5 hours of vigorous exercise per week (Appendix 2)

Other lifestyle factors:

- Avoid obesity (BMI >35 Kg/m^2)
- Avoid being underweight (BMI <19 Kg/m^2)
- Limit or stop drinking alcohol
- Stopping smoking, if relevant
- Taking regular gentle sun exposure ,without burning (Appendix 3)

Diet:

Aim for a healthy, varied diet avoiding fads and ensuring adequate intake of vitamins, essentially minerals, fibre, essentially fatty acids and antioxidants (Appendix 3):

- Eat more
    - Green and cruciferous vegetables
    - Fruits and berries
    - Nuts and grains
    - Healthy oils; (unsaturated fats, omega 3)
- Eat less
    - Unhealthy fats (saturated fats)
    - Carcinogenic containing foods

Vitamin and mineral supplements should not be required if individuals are able to eat a varied balanced diet. This review found no evidence suggesting that they can improve cancer outcomes and in fact, a studies involving vitamin A and E increased subsequent lung cancer risks as well as cardiac and cerebral vascular morbidity. Patients who took regular zinc supplement for long periods of time were found to have a higher risk of prostate cancer. Furthermore Folic acid and Vitamin B increased the cancer risk if given to patients after myocardial infarction. There is, however, evidence from cohort and prevention studies showed that individuals with vitamin or essential deficiencies had a higher incidence of cancer and the risk diminishes following specific nutritional correction with supplements. The evidence suggests therefore that if individuals are deficient in a vitamin or mineral they have an increased risk of cancer but if they take supplements with normal baseline levels the subsequent excess also increases the risk of cancer. It appears therefore that a normal level rather than high or low is ideal. These nutrients, however, are not measured in routine clinical practice but ideally, future trial designs should include bespoke patient analysis to identify those individuals with sub-clinical deficiencies. Fish oil supplement are a good way to increase omega 3 intake but there are no trials to suggest they help relapse rates although one study suggest they could help arthralgia. There may be a role for nutritional supplements which contains antioxidants such as lycopene, pomegranate or higher intake of green but trials have so far had relatively small numbers. They should not be taken during chemotherapy as they can interact with its mechanism of action. In summary, there may be a role for nutritional supplements but they need to be individualised to the needs of each patients and subject to further investigation before they can be recommended routinely.

How to Integrate Self-Management Lifestyle Strategies into Routine Management

Adopting a paternalistic approach and simply telling people is not enough. If the medical community want to help their patients embark on a road of recovery which includes regular exercise, there has to be a comprehensive and well funded package of education, guidance and support. Although some individuals may have exercised enthusiastically before their diagnosis they may not have the same motivation or abilities afterwards. The cancer itself, surgery, or the anticancer therapies, have resulted in physical disability, notwithstanding the commonly associated fatigue, lethargy, weight gain and reduced esteem in body image. Patient survivors may have to relearn their lifestyle and exercise patterns and consider a broad range of activities, particularly those which previously they may not have considered. The two fundamental approaches to encouraging patients to change their lifestyles to the better are: 1) Information provision, and 2) Supervised rehabilitation programmes.

1) Patient Information Provision

Evidence based information, emphasising the importance of lifestyle, ideally should be formally introduced into routine clinical practice early in the treatment pathway and re-enforced at regular intervals thereafter. This ensures patients and their relatives do not miss the teachable moment where they are most susceptible to positive advice (Demark-Wahnefried et al., 2005). This requires close work with clinicians, specialist nurses, patients and advocacy groups to enable information about new strategies to be integrated into existing local information pathways and materials. Indeed, the new information prescriptions currently being pilot tested provide ample opportunity for integrating lifestyle advice into survivorship care plans (Office for Public Management, University of York, and

GfK NOP for DH, 2008). As the level and complexity of information provided to patients and their relatives, who originate from a wide range of educational, cultural and religious backgrounds, increases a wide range of multimodal materials may need to be considered including DVD, websites, blogs and mobile phones (Thomas et al – video paper).

Before investing time and money on patient information materials, a vital first step is to convince the consultants, other direct clinical staff and organisers of clinical services that lifestyle advise is a priority and to re-allocate resources to enable sufficient time to discuss these issues within routine consultations. One study, for example, found that patients who were encouraged by their oncologist, exercised significantly more than patients who did not (Segar et al., 1998). As well as further scientific research, this may require a degree of lobbying from organisations such as Macmillan as well as formal teaching programmes, conferences, local lectures and courses. The next step is to back up the medical consultation with further practical verbal and written advice from specialist nurses or information officers. One UK oncology unit, for example, does this as part of a formal lifestyle interview together with a bespoke lifestyle information toolbox (Thomas, Taylor, and Williams, 2009). During this interview patients, can be referred to smoking cessation clinics, nutritionalist, and physiotherapist where necessary. The specialist nurse conducting this interview provides written information and advice to patients, and just as importantly their friends and family, about local support groups, dietary measures, where to buy healthy foods and specific local exercise facilities which may entice them ranging from ballroom, line and salsa dance lessons, aerobics, yoga and fitness classes, local walking, swimming and cycling groups through to gyms, sport centre, tennis and badminton courts, and pilates classes, giving times, contact numbers and locations to make it as easy as possible to follow the advice. The rationale for these interviews is that individualised lifestyle counselling is more likely to elicit a response, than generic general advice. The specialist nurse then follows up the advice by telephone and further consultations as prompting has been shown to improve update. A study from North Bedfordshire, for example, showed that although 52% of patients accepted referral for exercise in a local Gym a further 23% decided to attend classes only after additional prompting from the nurse either by telephone.

Many UK Oncology Units already have instigated an exit interview system to discuss follow up arrangements and this process could be expanded to include lifestyle counselling provided the specialist nurses involved have received extra training. This training should include a knowledge of the evidence and importance of diet, lifestyle and exercise after cancer as well as ways to appropriately advise home-based exercise regimens and how to direct patients towards the myriad of council or independent exercise activities available locally to them. The courses may require additional communication and motivational skills training to enable nurses to adapt advice depending on their client's cultural, psychological and physical preferences.

2) Supervised Exercise Rehabilitation

Experience from the more mature cardiac rehabilitation programs tells us that encouragement to exercise and improve other lifestyle factors based on written information alone is not enough (Oldridge et al., 1998, Ades, Huang, and Weaver, 1992). Various schemes have been investigated to improve motivation to exercise ranging from diaries to reminder wrist bands (refs). But the most powerful factors to improving physical activity is direct personal, supervision and support especially if lifestyle changes are to be sustained for long term benefit (Jolliffe et al., 2000; Quadrilatero and Hoffman-Goetz, 2003; Haydon et al., 2006). This especially applies to patients surviving cancer who have endured fundamental changes in their aspirations and abilities following their treatment or where

the cancer itself may have caused physical disability, fatigue, weight gain and reduced esteem in body image. The evidence from the review of cancer related fatigue also showed that supervised programmes were significantly more likely to result in a higher level of overall exercise and improvements in fatigue (Velthuis et al., 2009).

In practical terms this means a national network of supervised exercise and lifestyle courses which patients can be referred to during or following their adjuvant treatment as part of a formal cancer rehabilitation programme. In the USA such programmes for patients and their relatives are firmly established with the most well known established in the Rocky Mountains (Sprod, 2009). Although, more evidence is necessary to establish the relevance and timing of a formal rehabilitation programmes, initial data is encouraging. Rogers et al. (2009) evaluated the effectiveness of a 12-week physical activity course for breast cancer survivors. Forty-one women with stage I, II, or IIIA breast cancer who had completed primary chemotherapy and radiotherapy currently receiving hormonal therapy were randomly assigned to receive the 12-week supervised exercise or usual care. The intervention resulted in statistically significant sustained improvements in physical activity, strength, central adiposity, and social well-being measured at baseline and at 3 months. These benefits were also sustained at least up to 3 months after 3 months after intervention completion particularly in the measurement of lower extremity function (Rogers et al., 2009). There is further evidence that patients find exercise in their local gym acceptable. A study in north Bedfordshire referred 60 patients post chemotherapy and radiotherapy to designated municipal gyms for 24 supervised exercise sessions with a personal trainer. Eight percent declined the referral initially, 52% contacted gyms after initial referral and a further 23% contacted gyms only after prompting. Of the 75% proceeded to exercise sessions all completed the course (Thomas, Taylor, and Williams, 2009). A questionnaire at 12 weeks revealed that over 50% had never been to a gym before, the rate of good or excellent satisfaction was 94% and over 75% stated they would continue in the Gym after the scheme finished. Provided further training is forthcoming, suitably qualified personal trainers are also in an ideal position to continue the lifestyle advice started in the hospital setting.

Further research is needed to find out why these other 25% did not take up the offer of exercise supervision although there are already some indicators. For example, higher family support has been shown to be associated with a slower decline in physical activity in after taking part in an exercise intervention (Emery et al., 2009). Emotional health-related QoL following diagnosis with breast cancer also appears to be important for sustaining physical activity (Courneya et al., 2008), indicating that physical activity interventions among breast cancer survivors might be more successful if any depressive symptoms are addressed early in the course of treatment. Evidence is available of the effectiveness of telephone counselling in helping people to change exercise and dietary behaviours (Pierce et al., 2004). The benefits of self-management are also highlighted in evidence suggesting that survivors who self-refer themselves to a lifestyle intervention as opposed to being registry-ascertained show significantly greater increases in exercise at 1-year follow-up and significantly greater increases in fruit and vegetable consumption at both 1- and 2-year follow-up (Irwin et al., 2008; Snyder et al., 2008).

Where should exercise rehabilitation programmes be located?

The cardiac model is that patients recovering from myocardiac infarction have a 6 weeks, or more, formal exercise rehabilitation programme in hospital (Oldridge et al., 1998, Ades, Huang, and Weaver, 1992). They are then transferred via the national activity for health referral scheme to local

municipal Gyms. In the gyms patients, or at this stage more appropriately referred to as clients, are provided with exercise programmes supervised by exercise professional who have been specifically trained to a level 4 grade, determined by the organisation Skills Active (Sector for Skills Council for UK based leisure and learning).

Following the same hospital-initiated model for cancer rehabilitation would require considerable investment within hospitals in terms of money, space, time and extra physiotherapist. No doubt an in house rehabilitation scheme would be an advance for more complex or disabled patients and to get the ball rolling but may not be necessary for the majority who or undergoing or have completed adjuvant therapies or who have stable low volume metastatic disease. A significantly more cost effective scheme for the majority of patients would involve tapping into the existing national network of 5,700 municipal Gyms and their resident exercise professionals. For this reason, a joint application from Professor Thomas and a charitable organisation called the Wright foundation was submitted to Skills Active in October 2009. Following a national consultation process the template for designing courses for exercise professionals has now been accepted. This has paved they way for training organisations, such as The Wright Foundation, to start training exercise professional to a level 4 grade in cancer rehabilitation.

This level 4 training unit for exercise professional ensures they have a range of appropriate knowledge and skills to protect the patients/clients and themselves. These include communication skills; a good understanding of the principles of training and guidelines for teaching relevant to the cancer survivor; an understanding of the disease process and how it is managed; how physical activity influences the disease process; how the disease process influences the ability to safely exercise; the positive and negative aspects of physical activity on cancer; an understanding of cancer medications and their influence on the individual's ability to exercise; a knowledge of what to look out for during exercise, when to ask for help, when and how to feed back to the medical team.

The next step is to lobby the Department of Health to provide the finances to be able to integrate lifestyle counseling and supervised programmes within hospital and to expand the exercise referral scheme to include cancer as a primary indication. Further research would help persuade key decision makers, but in the mean time organisations such as Macmillan Cancer Support are in an ideal position to apply pressure for change based on the convincing evidence reviewed in this and other similar reports.

References

1. Ades PA, Huang D, Weaver SO (1992) Cardiac rehabilitation participation predicts lower rehospitalization costs. Am Heart J. 1992 Apr; 123(4 Pt 1):916-21.

2. Adlercreutz H, Fotsis T, and e.a. Bannwart C (1986) Urinary estrogen profile determination in young Finnish vegetarian and omnivorous women. J Steroid Biochem. 24: p. 289-95.

3. Allen, N. E., V. Beral, et al. (2009). "Moderate Alcohol Intake and Cancer Incidence in Women." J. Natl. Cancer Inst. 101(5): 296-305.

4. Amling C, Riffenburgh RH, Sun L, Moul JW, Lance RS, Kusuda L, Sexton WJ, Soderdahl DW, Donahue TF, Foley JP, Chung AK, McLeod DG. (2004) Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. J Clin Oncol., 22: p. 439-445.

5. Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. (2003) A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomarkers Prevent, 12: p. 64-67.

6. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA,Pearson L, Saibil F, van Stolk RU. (2003) A randomised trial of aspirin to prevent colorectal adenomas. The New England Journal of Medicine, 348(10): p. 891-899.

7. Battaglini C. (2004) A randomized study on the effects of a prescribed exercise intervention on lean mass and fatigue changes in breast cancer patients during treatment. Dissertation: *http://gateway.proquest.com/openurl%3furl_ver=Z39.88-2004%26res_dat=xri:pqdiss%26rft_val_fmt=info:ofi/fmt:kev:mtx:dissertation%26rft_dat=xri:pqdiss:3139617*

8. Baxter RC and Turtle JR (1978) Regulation of hepatic growth hormone receptors by insulin. Biochem Biophys Res Commun, 84: p. 350-7.

9. Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, Barnhill R. Sun exposure and mortality from melanoma. J Natl Cancer Inst 2005;97:195–9.

10. Blacklock CJ, Lawrence JR, Wiles D, Malcolm EA, Gibson IH, Kelly CJ, Paterson JR (2001) Salicylic acid in the serum of subjects not taking aspirin. Comparison of salicylic acid concentrations in the serum of vegetarians, non-vegetarians, and patients taking low dose aspirin. Journal of Clinical Pathology, 54: p. 553-555.

11. Blot WJ, Li J, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY, Liu BQ, Tangrea J, Sun YH, Liu F, Fraumeni JF, Zhang YH, Li B. (1993) Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J. Natl. Cancer Inst. (Bethesda), 85: 1483-1492.

12. Blutt SE, McDonnell TJ, Polek TC, Weigel NL. (2000) Calcitriol-induced apoptosis in LNCaP cells is blocked by overexpression of bcl-2. Endocrinology, 141: p. 10-17.

13. Campbell A, Mutrie N, White F, McGuire F,Kearney N.(2005) A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. Eur.J.Oncol.Nurs; 9:56-63.

14. Campell MJ, Koeffler HP (1997) Toward therapeutic intervention of cancer by vitamin D compounds. J Natl Cancer Inst, 89: p. 182-185.

15. Chan JM, Gann PH, and Giovannucci EL (2005) Role of diet in prostate cancer development and progression. Journal of Clinical Oncology, 23(32): p. 8152-60.

16. Chang PH, Lai YH, Shun SC et al. (2008) Effects of a walking intervention on fatigue-related experiences of hospitalized acute myelogenous leukemia patients undergoing chemotherapy: a randomized controlled trial. J Pain Symptom.Manage;35:524-

17. Chaudry AA, Wahle KWJ, McClinton S, Moffat LEF (1994) Arachidonic acid metabolism in benign and malignant prostatic tissue in vitro: Effects of fatty acids and cyclooxygenase inhibitors. Int J Cancer, 57: p. 176-180.

18. Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, van Breemen R, Ashton D, Bowen PE. (2001) Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. J Natl Cancer Inst, 93: p. 1872-1879.

19. Cheng, M (2009) Tanning beds are as deadly as arsenic, cancer study says. http://www.boston.com/news/nation/articles/2009/07/29/cancer_study_shows_tanning_beds_as_deadly_as_arsenic/.

20. Chlebowski R, Aiello E, and McTiernan A. (2002) Weight loss in breast cancer patient management. J Clin Oncol., 20: p. 1128-1143.

21. Chlebowski RT, Blackburn GL, Elashoff RE, Thomson C, Goodman MT, Shapiro A, Giuliano AE, Karanja N, Hoy MK, Nixon DW and The WINS Investigators (2005) Dietary fat reduction in post menopausal women with primary breast cancer. Journal of Clinical Oncology, (10): p. 3s.

22. Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, Slate EH, Witherington R, Herlong JH, Janosko E, Carpenter D, Borosso C, Falk S, Rounder J. (1998) Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. British Journal of Urology, 81: p. 730-734.

23. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D,Stewart B. (2003) Feasibility of exercise during treatment for multiple myeloma. Cancer Nurs;26:410-419.

24. Coombs GF (2004) Status of selenium in prostate cancer prevention. British Journal of Cancer, 91: p. 195-199.

25. Courneya KS, Segal RJ, Mackey JR et al. (2007) Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J.Clin.Oncol;25:4396-4404.

26. Courneya KS, Segal RJ, Gelmon K et al. (2007) Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy. Cancer Epidemiol.Biomarkers Prev.;16:2572-2578.

27. Cramp F,Daniel J.(2008) Exercise for the management of cancer-related fatigue in adults. Cochrane.Database.Syst.Rev. 2008;CD006145

28. Crowley S. (2003) The effect of a structured exercise program on fatigue, strength, endurance, physical self-efficacy, and functional wellness in women with early stage breast cancer;127.

29. Davies, N.J., Kinman, G., Thomas, R.J., and Bailey, T.A. (2008) Information satisfaction in breast and prostate cancer patients: Implications for quality of life. *Psycho-Oncology*, published online at http://www3.interscience.wiley.com/cgi-bin/abstract/117871474/ABSTRACT.

30. Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM (2005) Riding the Crest of the Teachable Moment: Promoting Long-Term Health After the Diagnosis of Cancer Journal of Clinical Oncology, Vol 23, No 24 (August 20), pp. 5814-5830.

31. Dieppe P, Ebrahim S, and Juni P (2004) Lessons from the withdrawl from rofecoxib. BMJ, 329: p. 867-868.

32. Dignam JJ, Polite B, Yothers G, Raich P, Colangelo L, O'Connell M and Wolmark N (2006) Effect of body mass index on outcome in patients with dukes B and C colon cancer: An analysis of NSABP trials. Journal of Clinical Oncology, 3533: p. 254s.

33. Dignam, J. J., B. N. Polite, et al. (2006). "Body Mass Index and Outcomes in Patients Who Receive Adjuvant Chemotherapy for Colon Cancer." J. Natl. Cancer Inst. 98(22): 1647-1654.

34. Drouin J, Krause S,Orr J. (2005) Effects of aerobic exercise training on Peak Aerobic Capacity, Fatigue, and Psychological factors during radiation for breast cancer. Rehabilitation Oncology;23:11-17.

35. Ebbing M, Bønaa, KH, Nygård O, Arnesen E, Ueland PM, Nordrehaug JE, Rasmussen K, Njølstad I, Refsum H, Nilsen DW, Tverdal A, Meyer K, Vollset SE

(2009) Cancer Incidence and Mortality After Treatment With Folic Acid and Vitamin B12 JAMA. 2009;302(19):2119-2126.

36. Egan KM, Stampfer MJ, Giovannucci E, Rosner BA, Colditz GA (1996) Prospective study of regular aspirin use and the risk of breast cancer. Journal of the National Cancer Institute, 88: p. 988-993.

37. Evans BA, Griffiths K, and Morton MS (1995) Inhibition of 5 alpha-reductase in genital skin fibroblasts and prostate tissue by dietary lignans and isoflavonoids. Journal of Endocrinology, 147: p. 295-302.

38. Figueiredo, J. C., M. V. Grau, et al. (2009). "Folic Acid and Risk of Prostate Cancer: Results From a Randomized Clinical Trial." J. Natl. Cancer Inst. 101(6): 432-435.

39. Flowers, M. and P. A. Thompson (2009). Conjugated Linoleic Acid Suppresses HER2 Protein and Enhances Apoptosis in SKBr3 Breast Cancer Cells: Possible Role of COX2." PLoS ONE 4(4): e5342.

40. Food and Drug Administration (FDA) (2006) Carcinogens and antioxidants.

41. Fraga CU (1991) Ascorbic acid protects against endogenous oxidative DNA damage in human sperm. Proc Nati Acad Sci USA, 8(8(24)): p. 11003.

42. Friedenreich CM, et al "Alberta physical activity and breast cancer prevention trial: Sex hormone changes in a year-long exercise intervention among postmenopausal women" *J Clin Oncol* 2010; DOI: 10.1200/JCO.2009.24.9557.

43. Freier S, Weiss O, Eran M, Flyvbjerg A, Dahan R, Nephesh I, Safra T, Shiloni E, Raz I. (1999) Expression of the insulin-like growth factors and their receptors in adenocarcinoma of the colon. Gut, 44: p. 704-8.

44. Fuchs C, Meyerhardt JA, Heseltine DL, Niedzwiecki D, Hollis D, Chan AT, Saltz LB, Schilsky RL and Mayer RJ (2005) Influence of regular aspirin use on survival for patients with stage III colon cancer: Findings from intergroup trial CALGB 89803. American Society of Clinical Oncology Abstract Book, 2005.

45. Giles GG and English DR (2002) The Melbourne Collaborative Cohort Study. IARC Sci Publ, 156: p. 69-70.

46. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. (2002) A prospective study of tomato products, lycopene, and prostate cancer risk. Journal of the National Cancer Institute, 94: p. 391-398.

47. Gold EB, Pierce JP, Natarajan L, Stefanick ML, Laughlin GA, Caan BJ, Flatt SW, Emond JA, Saquib N, Madlensky L, Kealey S, Wasserman L, Thomson CA, Rock CL, Parker BA, Karanja N, Jones V, Hajek RA, Pu M, and Mortimer JE. (2009) Dietary Pattern Influences Breast Cancer Prognosis in Women Without Hot Flashes: JCO vol 27, no.3; 352-359.

48. Golden, E. B., P. Y. Lam, et al. (2009). "Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors." Blood 113(23): 5927-5937.

49. Gong, Z., A. R. Kristal, et al. (2009). "Alcohol consumption, finasteride, and prostate cancer risk." Cancer 115(16): 3661-3669.

50. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N (2009) Prognostic Effects of 25-Hydroxyvitamin D Levels in Early Breast Cancer. Journal of Clinical Oncology, Vol 27, No 23 (August 10): pp. 3757-3763.

51. Gritz ER (1993) Cancer Smoking Epidemiology Biomarkers & Prevention, 2;(3); 261-270.

52. Gross M, Jo S, Huang D, Mirocha J, Shazer R, Holden S and Agus D (2006) Obesity, ethnicity and surgical outcome for clinically localized prostate cancer. Journal of Clinical Oncology, 5(9615 supplement): p. 865.

53. Hamilton M, Wolf J, Rusk J (2006) Effects of Smoking on the Pharmacokinetics of Erlotinib. Clinical Cancer Research doi: 10.1158/1078-0432.CCR-05-2235 Clinical Cancer Research April 1, 12, 2166.

54. Harris RE, Namboodiri KK, and Farrar WB. (1996) Nonsteroidal antiinflammatory drugs and breast cancer. Epidemiology, 7: p. 203-205.

55. Harvei S, Bjerve KS, Tretli S, Jellum E, Robsahm TE, Vatten L. (1997) Prediagnostic level of fatty acids in serum phospholipids: Omega-3 and omega-6 fatty acids and the risk of prostate cancer. Int J Cancer, 71(545-551).

56. Hayes SC, Spence RR, Galvao DA,Newton RU (2009) Australian Association for Exercise and Sport Science position stand: Optimising cancer outcomes through exercise. J.Sci.Med.Sport. 2009;12:428-434.

57. Haydon AM, Macinnis RJ, English DR, Giles GG. (2006) The effect of physical activity and body size on survival after diagnosis with colorectal cancer. Gut, 55: p. 62-67.

58. Headley JA, Ownby KK,John LD. (2004) The effect of seated exercise on fatigue and quality of life in women with advanced breast cancer. Oncol.Nurs.Forum; 31:977-983.

59. Heinen et al (2007) Antioxidant intake and skin cancer relapse. EJC 200, 2707-16

60. Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, Haapakoski J, Malila N, Rautalahti M, Ripatti S, Mäenpää H, Teerenhovi L, Koss L, Virolainen M, Edwards BK. (1998) Prostate cancer and supplementation with alpha-tocopherol and beta carotene: Incidence and mortality in a controlled trial. J Natl Cancer Inst, 90: p. 440-446.

61. Hippisley-Cox J and Coupland C (2005) Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. British Medical Journal, 330: p. 1366-1369.

62. Holick CN, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Bersch AJ, Stampfer MJ, Baron JA, Egan KM, and Willett WC (2008) Physical Activity and Survival after Diagnosis of Invasive Breast Cancer. Cancer Epidemiological Biomarkers Prev., PP. 379-386.

63. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. (1999) Dietary factors and the survival of women with breast cancer. Cancer, 85(5): p. 826-35.

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

65. Hsieh T and Wu JM, (1997) Induction of apoptosis and altered nuclear/cytoplasmic distribution of the androgen receptor and prostate-specific antigen by 1 alpha, 25-dihydroxyvitamin D3 in androgen-responsive LNCaP cells. Biochemical and biophysical research communications, 235: p. 539-544.

66. Hsu AL, Ching Tt, Wang DS, Song X, Rangnekar VM, Chen CS (2000) The cyclooxygenases-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2. Journal of Biological Chemistry, 275: p. 11397-11403.

67. Hwang JH, Chang HJ, Shim YH et al.(2008) Effects of supervised exercise therapy in patients receiving radiotherapy for breast cancer. Yonsei Med.J.;49:443-450.

68. Jackson MJ, Dillon SA, Broome CS, McArdle A, Hart CA, McArdle F. (2004) Are there functional consequences of a reduction in selenium intake in UK subjects? Proceedings of the Nutrition Society, 63: p. 513-517.

69. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S (2000) Exercise-based rehabilitation for coronary heart disease Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Cochrane Database Syst Rev.;(4):CD001800.

70. Joseph A, Moysich KB, Freudenheim JL, Shields PG, Bowman ED, Zhang Y, Marshall JR, and Ambrosone CB (2007) Cruciferous Vegetables, Genetic Polymorphisms in Glutathione S-Transferases M1 and T1, and Prostate Cancer Risk Michael A. NUTRITION AND CANCER, 50(2), 206–213.

71. Kaaks R and Lukanova A (2002) Effects of weight control and physical activity in cancer prevention: role of endogenous hormone metabolism. Ann N Y Acad Sci, 963: p. 268-81.

72. Klein A (2009) SELECT STUDY. JNCI Journal of the National Cancer Institute 2009 101(5):283-285.

73. Knekt P , Aromaa A , Maatela J , Alfthan G , Aaran R , Hakama M , Hakulinen T , Peto R , and Teppo L (1990) Serum Selenium and Subsequent Risk of Cancer Among Finnish Men and Women. J. Natl. Cancer Inst. 82: 864-868.

74. Knols R, Aaronson NK, Uebelhart D, Fransen J, Aufdemkampe G (2005) Physical exercise in cancer patients during and after medical treatment: A systemic review of randomised and controlled clinical trials. Journal of Clinical Oncology, 23(16): p. 3830-3842.

75. Kok FJ, De Bruun AM, Hofman A, et al. (1987) Is serum selenium a risk factor for cancer in men only? Am J Epidemiol 125:12-16, 1987.

76. Kortenkamp, A (2008) Breast cancer and exposure to hormonally active chemicals: An appraisal of the scientific evidence. A background briefing paper. ChemTrust, London, April 2008.

77. Kristal AR, Cohen JH, Qu P, Stanford JL. (2002) Associations of energy, fat, calcium and vitamin D with prostate cancer risk. Cancer Epidemiol Biomarkers Prevent, 11: p. 719-725.

78. Kroenke CH, et al., Dietary patterns and survival after breast cancer diagnosis. Journal of Clinical Oncology, 2005. 23(36): p. 9295-0303.

79. Kroenke CH, et al Weight gain and survival after breast cancer diagnosis. JCO 2005. **23**(7): p. 1370-1378

80. Kucuk O, Sarkar FH, Djuric Z, Sakr W, Pollak MN, Khachik F, Banerjee M, Bertram JS, Wood DP Jr. (2002) Effects of lycopene supplementation in patients with localized prostate cancer. Exp Biol Med (Maywood), 227: p. 881-885.

81. Lahmann PH, Friedenreich C, Schuit AJ, Salvini S, Allen NE, Key TJ, Khaw KT, Bingham S, Peeters PH, Monninkhof E, Bueno-de-Mesquita HB, Wirfält E, Manjer J, Gonzales CA, Ardanaz E, Amiano P, Quirós JR, Navarro C, Martinez C, Berrino F, Palli D, Tumino R, Panico S, Vineis P, Trichopoulou A, Bamia C, Trichopoulos D, Boeing H, Schulz M, Linseisen J, Chang-Claude J, Chapelon FC, Fournier A, Boutron-Ruault MC, Tjønneland A, Føns Johnson N, Overvad K, Kaaks R, Riboli E. (2007) Cancer Epidemiol Biomarkers Prev. Jan;16(1):36-42. Epub 2006 Dec 19.

82. Land, C. E. (1995). "Studies of Cancer and Radiation Dose Among Atomic Bomb Survivors: The Example of Breast Cancer." JAMA 274(5): 402-407.

83. Leatham A and Velentzis L (2006) DietComplyf: The role of diet, complementary treatment, and lifestyle in breast cancer survival. http://www.ucl.ac.uk/abc-research-group/Documentations/DietCompLyf%20Protocol%20v6,%20Jan%2006.pdf.

84. Lee CY (2002) Phytochemicals and apples. The Lancet. 359(12): p. 9301.

85. Lee MM, Gomez SL, Chang JS, Wey M (2003) Soy and Isoflavone Consumption in Relation to Prostate Cancer Risk in China. Cancer Epidemiology, Biomarkers & Prevention July 1, 2003 12, 665.

86. Li C, Daling J, Porter P, Tang M, Malone K 2009. Relationship between potentially modifiable lifestyle factors and risk of secondary contralateral breast cancer Journal of Clinical Oncology vol. 27, No.32, pp4312-5302

87. Lucia A, Earnest C, Perez M. (2003) Cancer-related fatigue: can exercise physiology assist oncologists? Lancet Oncol; 4:616-625.

88. Ma J, Giovannucci E, Pollak M, Leavitt A, Tao Y, Gaziano JM, Stampfer MJ. (2004) A prospective study of plasma C-peptide and colorectal cancer risk in men. J Natl Cancer Inst, 96: p. 546-53.

89. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ. (1999) Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGFbinding protein-3. J Natl Cancer Inst, 91: p. 620-5.

90. Madaan S, Abel PD, Chaudhary KS, Hewitt R , Stott MA, Stamp GWH and Lalani EN (2000) Cytoplasmic induction and over-expression of cyclooxygenase-2 in human prostate cancer: implications for prevention and treatment. International Journal of Urology, 86: p. 736-741.

91. Mahmud S, Franco E, and Aprikian A. (2003) Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. British Journal of Cancer. 90: p. 93-99.

92. Marklund SL, Westman NG, Lundgren E, Roos G. (1982) Copper- and zinc-containing superoxide dismutase, manganese-containing superoxide dismutase, catalase, and glutathione peroxidase in normal and neoplastic human cell lines and normal human tissues. Cancer Research, 42(5): p. 1955-61.

93. Mehta RG and Moon RC (1991) Characterization of effective chemopreventive agents in mammary gland in vitro using an initiation-promotion protocol. Anticancer Research, 11: p. 593-596.

94. McLarty, Jerry, Bigelow, Rebecca L.H., Smith, Mylinh, Elmajian, Don, Ankem, Murali, Cardelli, James A. (2009) Tea Polyphenols Decrease Serum Levels of Prostate-Specific Antigen, Hepatocyte Growth Factor, and Vascular Endothelial Growth Factor in Prostate Cancer Patients and Inhibit Production of Hepatocyte Growth Factor and Vascular Endothelial Growth Factor In vitro. Cancer Prev Res: 1940-6207.CAPR-08-0167.

95. McTiernan A, Ulrich C, Slate S, Potter J. (1998) Physical activity and cancer etiology: associations and mechanisms. Cancer Causes Control, 9: p. 487-509.

96. Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Schilsky RL and Fuchs CS (2005) The impact of physical activity on patients with stage III colon cancer: Findings from Intergroup trial CALGB 89803. Proc Am Soc Clin Oncol, 24: p. abstract 3534.

97. Minton O, Stone P (2009). A systemic review of the sacles used for the measurement of cancer-related fatigue. Annals of Oncology, 20, 17-25.

98. Mock V, Burke MB, Sheehan P et al. (1994) A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. Oncol.Nurs.Forum;21:899-907.

99. Mock V, Pickett M, Ropka ME et al. (2001) Fatigue and quality of life outcomes of exercise during cancer treatment. Cancer Pract. 9:119-127.

100. Mock V, Frangakis C, Davidson NE et al.(2005) Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. Psychooncology;14:464-477.

101. Monga U, Garber SL, Thornby J et al. (2007) Exercise prevents fatigue and improves quality of life in prostate cancer patients undergoing radiotherapy. Arch.Phys.Med.Rehabil;88:1416-1422.

102. Mutrie N, Campbell AM, Whyte F et al. (2007) Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. BMJ;334:517.

103. National Comprehensive Cancer Network (2009) NCCN Clinical Practice Guidelines in Oncology. Cancer-related fatigue, version 1. 2009.

104. Nomura AM, et al. (2003) Serum insulin-like growth factor I and subsequent risk of colorectal cancer among Japanese-American men. Am J Epidemiol, 158: p. 424-31.

105. Ng, K., J. A. Meyerhardt, et al. (2008). "Circulating 25-Hydroxyvitamin D Levels and Survival in Patients With Colorectal Cancer." J Clin Oncol 26(18): 2984-2991.

106. Nguyen, T. and D. Ho (2002). "Nonmelanoma skin cancer." Current Treatment Options in Oncology 3(3): 193-203.

107. Oldridge NB, Guyatt GH, Fischer ME, and Rimm AA (1988) Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. JAMA vol.2 60, 7.

108. Omenn GS, et al., (1996) Risk factors for lung cancer and for intervention effects in CARET, the beta-carotene in retinol efficacy trial. Journal of the National Cancer Institute, 88: p. 1550-1559.

109. Onland-Moret, N. C., P. H. M. Peeters, et al. (2005). "Alcohol and Endogenous Sex Steroid Levels in Postmenopausal Women: A Cross-Sectional Study." J Clin Endocrinol Metab 90(3): 1414-1419.

110. Ornish D, et al. (2005) Intensive lifestyle changes may affect the progression of prostate cancer. The Journal of Urology, 174: p. 1065-1070.

111. Ostroff JS, Jacobsen PB, Moadel AB, Spiro RH, Shah JP, Strong EW, et al. (1995) Prevalence and predictors of continued tobacco use after treatment of patients with head and neck cancer. Cancer; Jan 15;75(2):569-76.

112. Palmqvist R, et al., (2002) Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: a prospective study in northern Sweden. Gut, 50: p. 642-6.

113. Pantuck AJ, et al. (2006) Phase 11 study of pomegranate juice for men with rising PSA following surgery or RXT for prostate cancer. Clin Cancer Res, 12(13): p. 4018-4026.

114. Payne JK, Held J, Thorpe J,Shaw H. (2008) Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol.Nurs.Forum; 35:635-642.

115. Peehl DM, et al. (1994) Antiproliferative effects of 1, 25-dihydroxyvitamin D3 on primary cultures of human prostatic cells. Cancer Research, 54: p. 805-810.

116. Pierce, J. P., L. Natarajan, et al. (2007). "Influence of a Diet Very High in Vegetables, Fruit, and Fiber and Low in Fat on Prognosis Following Treatment for Breast Cancer: The Women's Healthy Eating and Living (WHEL) Randomized Trial." JAMA 298(3): 289-298.

117. Quadrilatero J and Hoffman-Goetz L, (2003) Physical activity and colon cancer. Asystematic review of potential mechanisms. J Sports Med Phys Fitness, 43: p. 121-138.

118. Reeves G, Pirie K, Beral V et al (2007) Cancer incidence andmortality in relation to BMI in the Million Women Study. BMJ, 335, 1134.

119. Richardson, G. E., M. A. Tucker, et al. (1993). "Smoking Cessation after Successful Treatment of Small-Cell Lung Cancer Is Associated with Fewer Smoking-related Second Primary Cancers." Annals of Internal Medicine 119(5): 383-390.

120. Rier SE, Martin DC, Bowman RE, Dmowski WP, Becker JL (1993), Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fundam Appl Toxicol 21:433-441 (1993).

121. Rodriguez C et al, (2004) Vitamin E supplements and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prevent, 13: p. 378-382.

122. Rogers L, Hopskin-Price, Vicari et al. (2009) Physical Activity and Health Outcomes Three Months After Completing a Physical Activity Behavior Change Intervention: Persistent and Delayed Effects. Cancer Epidemiol Biomarkers Prev, 18(5):1410–8.

123. Rohan TE, Hiller JE, and McMichael AJ. (1993) Dietary factors and survival from breast cancer. Nutr Cancer, 1993. 20: p. 167-77.

124. Rose DP (1992) Dietary fibre, phytoestrogens and breast cancer. Nutrition, 8: p. 47-51.

125. Sandler RS, et al. (2003) A randomised trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. The New England Joural of Medicine, 348(10): p. 883-890.

126. Schmitz K, Ahmed R, Troxel A, A Cheville A, Smith R, LLewis-Grant, Bryan C, Q. Greene 2009 Weight lifting programmes for women post axillary node clearance reduces lymphoedema related events. New England Journal of Medicine Vol 361: 664-673 no.7.

127. Schoonen WM, et al. (2005) Alcohol cosumption and the risk of prostate cancer in middle-aged men. Int J Cancer, 113: p. 133-140.

128. Schreinemachers DM and Everson RB. (1994) Aspirin use and lung, colon and breast cancer incidence in a prospective study. Epidemiology, 5: p. 138-146.

129. Schwartz GG et al. (1994) Human prostate cancer cells: Inhibition of proliferation by vitamin D analogs. Anticancer Research, 1994. 14: p. 1077-1081.

130. Schwartz, L. H., M. Ozsahin, et al. (1994). "Synchronous and metachronous head and neck carcinomas." Cancer **74**(7): 1933-1938.

131. Schwarz S, Obermu UC, ller-Jevic, Hellmis E, Koch W, Jacobi G, and Biesalski HK (2008) Lycopene Inhibits Disease Progression in Patients with Benign Prostate Hyperplasia. Journal of nutrition and disease J. Nutr. 138: 49–53, 2008.

132. Scripture CD and Figg WD (2006) Drug interactions in cancer therapy. *Nature Reviews Cancer* **6**, 546–558 (1 July 2006).

133. Segal RJ, Reid RD, Courneya KS et al.(2003) Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J.Clin.Oncol.;21:1653-1659.

134. Segal RJ, Reid RD, Courneya KS et al.(2009) Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol.;20;27:344-351.

135. Segar M, et al. (1998) The affect of aerobic exercise on self-esteem and depressive and anxiety symptoms among breast cancer survivors. Oncol Nurs Forum, 25: p. 107-113.

136. Smedby KE, Hjalgrim H, Melbye M, Torrång A, Rostgaard K, Munksgaard L, et al.(2005) Ultraviolet radiation exposure and risk of malignant lymphomas. J Natl Cancer Inst;97:199–209.

137. Soliman, S., W. J. Aronson, et al. (2009). "Analyzing Serum-Stimulated Prostate Cancer Cell Lines After Low-Fat, High-Fiber Diet and Exercise Intervention." eCAM: nep031.

138. Sonn GA, Aronson W, and Litwin MS (2005) Impact of diet on prostate cancer: A review. Prostate cancer and prostate disease, 8: p. 304-310.

139. Spentzos D, Mantzoros C, Regan MM, Morrissey ME (2003) Clinical Cancer Research August 2003 9, 3282.

140. Sprod LK (2009) Considerations for Training Cancer Survivors Strength and conditioning journal volume 31, number 1. Rocky Mountain Cancer Rehabilitation Institute, University of Northern Colorado, Greeley, Colorado.

141. Stivala LA, et al. (2000) The antiproliferative effect of beta-carotene requires p21waf1/cip1 in normal human fibroblasts. Journal of Biochemistry, 267: p. 2290-2296.

142. Suikkari AM, et al. (1988) Insulin regulates the serum levels of low molecular weight insulin-like growth factor-binding protein. J Clin Endocrinol Metab, 66: p. 266-72.

143. Svilaas A, et al. (2004) Intake of antioxidants in coffee, wine and vegetables are correlated with plasma carotenoids in humans. Journal of Nutrition, 134: p. 562-567.

144. Terry P, et al. (2001) Fatty fish consumption and risk of prostate cancer. Lancet, 357: p. 1764-1766.

145. Terry PD, Rohan TE, and Wolk A (2003) Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: A review of the epidemiologic evidence. American Journal of Clinical Nutrition, 77: p. 532-543.

146. Thomas R, Daly M, and Perryman J (2000) Forewarned is forearmed - Randomised evaluation of a preparatory information film for cancer patients. European Journal of Cancer, 36(2): p. 52-53.

147. Thomas R, et al. (2005) Dietary advice combined with a salicylate, mineral and vitamin supplement (CV247) has some tumour static properties - a phase II study. Nutrition and science, 2005. 35(6): p. 436-451.

148. Thomas R et al. (2006) Diet, salicylates and Prostate cancer. British Journal of Cancer Management,.

149. Thomas R and Davies N (2007) Cancer – the roles of exercise in prevention and progression. Nutrition and Food Science, Volume 37; Issue 5.

150. Thomas R and Davies N (2007) Lifestyle during and after cancer Treatments. Clinical Oncology, 19, pp 616-627.

151. Thomas R, Blades M, Williams M (2007) Can dietary intervention alter prostate cancer progression. Nutrition & Food Science, 2007 vol 37, no.1 pp 24-36.

152. Thomas R (2008) Lifestyle after cancer – the facts. Health Education Publications (www.cancernet.co.uk/books.htm)

153. Thomas R, Williams M, and Davies N (2009) Should oncology units establish Lifestyle Clinics? Clinical Focus on Cancer Medicine, (1) 2; 38-48.

154. Thomas R, Taylor T, Williams M (2009) Development of a lifestyle exit tool box abstract and poster. ECCO, EJC vol 7, no.2, p.210; sup.3608.

155. Thomas R, Williams M, and Taylor T (2009) Life after cancer – rehabilitation at home can improve well-being and survival. *British Journal of Home Healthcare*, 5(1):10-12.

156. Thomas R (2009) Exercise after Cancer – How to do it? ICAN Journal; September 2009.

157. Thun, M. J., R. Peto, et al. (1997). "Alcohol Consumption and Mortality among Middle-Aged and Elderly U.S. Adults." N Engl J Med **337**(24): 1705-1714.

158. van der Bol JM, Mathijssen RHJ, Loos WJ, Friberg LE, van Schaik RHN, de Jonge MJA, Planting AS, Verweij J, Sparreboom A, de Jong FA. (2007) Cigarette Smoking and Irinotecan Treatment: Pharmacokinetic Interaction and Effects on Neutropenia. Journal of Clinical Oncology, Vol 25, No 19 (July 1), pp. 2719-2726.

159. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM (in press) The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of Randomised Controlled Trials Clinical Oncology, 2009 (in print).

160. Wagner LI, Cella D. (2004) Fatigue and cancer: causes, prevalence and treatment approaches. Br.J.Cancer;91:822-828.

161. Warren RS, et al. (1996) Induction of vascular endothelial growth factor by insulin-like growth factor 1 in colorectal carcinoma. J Biol Chem, 271: p. 29483-8.

162. Westerlind KC (2003) Physical activity and cancer prevention-mechanisms. Med Sci Sports Exerc., 2003. 35: p. 1834-40.

163. Wilkinson S and Chodak GW, (2003) Critical review of complementary therapies for prostate cancer. Journal of Clinical Oncology, 21(11): p. 2199-2210.

164. Windsor PM, Nicol KF,Potter J. (2004) A randomized, controlled trial of aerobic exercise for treatment-related fatigue in men receiving radical external beam radiotherapy for localized prostate carcinoma. Cancer;101:550-557.

165. Wu A, Pike M, and Stram D (1999) Dietary fat intake, serum estrogen levels, and the risk of breast cancer. J Natl Cancer Inst, 91: p. 529-534.

166. Yu GP et al. (1997) The effect of smoking after treatment for Cancer. Cancer Detect Prev 21:487-509.

167. Yu H and Rohan T (2000) Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst; 92: p. 1472-89.

168. Zhao XY, et al. (1999) Induction of androgen receptor by 1 alpha, 25-dihydroxyvitaminD3 and 9-cis retinoic acid in LNCaP human prostate cancer cells. Endocrinology, 140: p. 1205-1212.

169. Garssen B. Psychological factors and cancer development: Evidence after 30 years of research. *Clinical Psychology Review* 2004; 24(3):315–338.

170. Dalton SO, Boesen EH, Ross L, Schapiro IR, Johansen C. Mind and cancer: Do psychological factors cause cancer? *European Journal of Cancer* 2002; 38(10):1313–1323.

171. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. *The Lancet Oncology* 2004; 5(10):617–625.

172. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: Pathways and mechanisms. *Nature Reviews Cancer* 2006; 6(3):240–248.

173. Andersen BL, Farrar WB, Golden-Kreutz D, et al. Stress and immune responses after surgical treatment for regional breast cancer. *Journal of the National Cancer Institute* 1998; 90(1):30–36.

174. Thaker PH, Han LY, Kamat AA, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nature Medicine* 2006; 12(8):939–944.

Appendix 1

Summary of self help dietary strategies to improve the odds of better cancer outcomes

Food	Advice
Reduce Saturated Fats	Unless underweight, avoid processed fatty foods, cakes, biscuits, crisps and other fatty snacks, pastries, cream, and fried foods. Cut the fat off the meat and check serum cholesterol regularly.
Meat and intake	Use meat for its taste, preferably not more than once a day. Remove excess fat gently grill rather than fried to further reduce the fat content and avoid burning. If extra oil is needed use vegetable oils rather than animal fat. Increase fibre intake when eating meat such as salad and vegetables
Increase all fish intake	All fresh fish, but particularly the oily varieties such as mackerel and sardines. Fresh water fish such as trout have the advantage of avoiding the potential heavy metal contamination of tuna & sword fish which some suggest should not be eaten more than twice a week.
Reduce Exposure to Potential Carcinogens	Try to avoid heavily processed foods, which often contain high concentrations of fat, salt, sugar and food additives. Wash salads and vegetables thoroughly to avoid airborne chemicals, which may have settled on them. Avoid excessive amounts of foods containing high levels of aromatic hydrocarbons and acrylamides such as smoked food or those associated with high temperature cooking processes such as deep fried foods, crisps, chips, barbecued, and heavily fried meats.
Essential minerals	Vary the diet to ensure intake of adequate quantities of essential minerals consider; Mixed nuts, including Brazils; Seafood including sardines, prawns and shell fish; Pulses and grains. Vary carbohydrate

	sources such as pasta, rice, different brands of potatoes, pulses such as lentils and quinoa.
Dietary Vitamins	Fresh fruit, raw and calciferous vegetables, grains, oily fish, nuts and salads. Unless you have diarrhoea try to increase the amount of ripe fruit you eat each day, ideally by eating the whole fruit. Freshly squeezed fruit juices are recommended.
Polyphenols	Onions, leeks, broccoli, blueberries, red wine, tea, apricots, pomegranates, chocolate, coffee, blueberries, kiwis, plums, cherries, ripe fruits, parsley, celery, tomatoes, mint, citrus fruit.
Phytoestrogens	Soybeans and other legumes including peas, lentils, pinto (baked beans), and other beans and nuts (supplements not recommended).
Non-oestrogenic Polyphenols	Skin of colourful foods such as cherries, strawberries, blackcurrant, blackberries, dates, cranberries, red grapes, white button mushrooms.
Lignans & Stilbens	Flaxseed, linseeds, hemp nuts, grains.
Increase Carotenoids (Lycopene)	Tomatoes, tomato sauce, chilli, carrots, green vegetables and dark green salads.

Appendix 2

Table to summarise tips to increase daily exercise activities

Category	Lifestyle Advice
Generally	Exercise should not just be a passing fad but be incorporated into our daily lives for the rest of our lives. During the day we have several choices, which require more or less levels of exertion. Try to take the more active option, such as walking instead of using the car for short journeys or getting off the bus or tube one stop earlier.
Home	If you like exercising at home it is worth having a semi-formal programme to follow. There are many useful gadgets available to make it more fun (exercise bikes, treadmills, rowing machines, etc). Alternatively, follow an exercise video - there are many good ones available. When watching TV try to get up and walk around for a few minutes at every break.
Office	Use the stairs instead of the lift. If possible take a walk at lunchtime. Try desk exercises - You may look odd but they can keep you alert especially when you get tired or sleepy. Do not worry about the comments - people will secretly admire your enthusiasm.
Social Life	There is an alternative to the pub or the TV. Exercise can and should be sociable and enjoyable - find something which is fun otherwise you will give it up very quickly.
Walking	In addition to integrating walking into our daily routine, social walking groups are available in many areas and are a good way to meet new people, view interesting scenery and exercise to a variety of ability levels. Golf is a good encouragement to walk and clubs are available throughout Britain for all levels.
Cycling	Cycling socially with family or part of a daily commute, even if only once or twice a week, can be fun and even save money. Consider buying a bike with a

	basket for the shopping.
Gym	Joining a gym is always a good start. Paying money every month is a good incentive to use it. Even if you are overweight or unfit don't worry as so are most other people and nobody of worth will criticise your efforts. In some area there are exercise referral schemes to special instructors - ask your GP
Exercise Classes	There are numerous enjoyable ways to exercise in groups at a variety of levels. Your local sports centre will also have many activities from 5-aside football, squash, badminton, volleyball, netball, and numerous exercise aerobics classes.
Swimming	Many pools offer classes to learn to swim; they often offer single sex or disabled and disabled classes.
Dance	There are numerous dance classes available in most towns, from traditional ballroom and line dancing to rock & roll or salsa.

Cancernet.co.uk/exercise is able to search for a range of activities by postcode, providing times, contact numbers and locations.

Appendix 3

Table to summarise tips to encourage healthy eating

Food	Advice
Reduce Saturated Fats	Avoid processed fatty foods, cream, and fried foods. Check serum cholesterol.
Reduce Meat Intake	Use meat for its taste, preferably not over once a day. Excess fat should be removed and the meat gently grilled rather than fried to further reduce the fat content and avoid burning. If extra oil needs to be used in cooking, use olive oil rather than animal fat.
Increase all fish intake	All fresh fish, but particularly the oily varieties such as mackerel and sardines. Fresh water fish such as trout have the advantage of avoiding the potential heavy metal contamination of tuna & sword fish which some suggest should not be eaten more than twice a week.
Reduce Exposure to Potential Carcinogens	Try to avoid heavily processed foods, which often contain high concentrations of fat, salt, sugar and food additives. Reducing the amount of time that vegetables are cooked should maintain the flavour. Wash salads and vegetables thoroughly to avoid pesticides and airborne chemicals, which may have settled on them. Organic foods reduce the pesticide exposure further. Avoid excessive amounts of foods containing high levels of aromatic hydrocarbons and acrylamides such as smoked food or those associated with high temperature cooking processes such as deep fried foods, crisps, chips, barbecued, and heavily fried meats.
Increase Dietary Selenium	Brazil nuts, sardines, prawns; 60-75mcg/day; no more than 200mcg/day.
Avoid Excessive Calcium and Zinc	Unless prescribed for other reasons avoid supplements which give more than 1500mg of calcium and 11mg zinc per day.
Increase Dietary Vitamins	Fresh fruit, raw and calciferous vegetables, grains, oily fish, nuts and salads. Unless you have diarrhoea try to increase the amount of ripe fruit you eat each day, ideally by eating the whole fruit. Freshly squeezed fruit juices.
Polyphenols	Onions, leeks, broccoli, blueberries, red wine, tea, apricots, pomegranates, chocolate, coffee, blueberries, kiwis, plums, cherries, ripe fruits, parsley, celery, tomatoes, mint, citrus fruit.
Phytoestrogens	Soybeans and other legumes including peas, lentils, pinto (baked beans), and other beans and nuts (supplements not recommended).
Non-oestrogenic Polyphenols	Skin of colourful foods such as cherries, strawberries, tannins (red wine), blackcurrant, blackberries, dates, cranberries, red grapes, white button mushrooms.
Lignans & Stilbens	Flaxseed, linseeds, hemp nuts, grains.
Increase Carotenoids (Lycopene)	Tomatoes, tomato sauce, chilli, carrots, green vegetables and dark green salads.