



OPEN ACCESS

Exercise-induced biochemical changes and their potential influence on cancer: a scientific review

Robert James Thomas,¹ Stacey A Kenfield,² Alfonso Jimenez³

¹Primrose Oncology Unit, Bedford Hospital NHS Trust, Bedford, UK

²Department of Urology, University of California, San Francisco, California, USA

³Centre for Applied Biological and Exercise Sciences, Faculty of Health and Life Sciences, Coventry University, Coventry, UK

Correspondence to

Professor Robert James Thomas, Primrose Oncology Unit, Bedford Hospital NHS Trust, Kempston Road, Bedford MK42 9DJ UK; rt@cancernet.co.uk

Accepted 19 November 2016

ABSTRACT

Aim To review and discuss the available international literature regarding the indirect and direct biochemical mechanisms that occur after exercise, which could positively, or negatively, influence oncogenic pathways.

Methods The PubMed, MEDLINE, Embase and Cochrane libraries were searched for papers up to July 2016 addressing biochemical changes after exercise with a particular reference to cancer. The three authors independently assessed their appropriateness for inclusion in this review based on their scientific quality and relevance.

Results 168 papers were selected and categorised into indirect and direct biochemical pathways. The indirect effects included changes in vitamin D, weight reduction, sunlight exposure and improved mood. The direct effects included insulin-like growth factor, epigenetic effects on gene expression and DNA repair, vasoactive intestinal peptide, oxidative stress and antioxidant pathways, heat shock proteins, testosterone, irisin, immunity, chronic inflammation and prostaglandins, energy metabolism and insulin resistance.

Summary Exercise is one of several lifestyle factors known to lower the risk of developing cancer and is associated with lower relapse rates and better survival. This review highlights the numerous biochemical processes, which explain these potential anticancer benefits.

INTRODUCTION

Exercise is one of several lifestyle factors known to lower the risk of developing cancer.^{1–8} Moreover, the benefits of exercise continue after diagnosis. There is increasingly convincing evidence that, especially within supervised programmes, exercise mitigates many of the adverse toxicities common among cancer survivors and improves overall quality of life.^{9–12} Observational cohort studies of patients diagnosed with cancer have also linked regular exercise, either at the work place or domestic physical activity, with a lower probability of relapse or cancer-specific death after initial radical treatments.^{13–19} As there is a deficiency of randomised data, some could argue that cohort studies are merely observing habit-forming linkages. People who exercise, for example, are less likely to smoke, have a healthier body mass index (BMI) and eat more vegetables.²⁰ Although this remains a possibility, most analyses have adjusted for other lifestyle behaviours that may be associated with exercise and the outcome (potential confounders) using multivariate analysis, and the association of exercise with cancer outcomes in diverse patient populations shows high consistency.^{19 21–24}

The lack of randomised control trials (RCT) data for clinical end points (ie, progression, death) is being addressed by ongoing studies such as the CHALLENGE study (Colon Health and Life-Long Exercise Change),²⁵ the INTERVAL-MCRPC study (Intense Exercise for Survival among men with Metastatic Castrate-Resistant Prostate Cancer)²⁶ and the PANTERA study (Exercise as Treatment for Men with Prostate Cancer) starting enrolment in 2016. The precise mechanisms elucidating the anticancer effects of exercise have not been fully established; biomarker analyses within these trials as well as additional preclinical experimental data will provide critical supporting evidence. In the mean time, this article summarises the available international literature and discusses the potential indirect and direct biochemical mechanisms of how physical activity (exercise) could positively, or negatively, influence oncogenic pathways.

METHODOLOGY

In this scientific review, we searched for published trials assessing the biological changes that occur after physical activity, which could influence cancer-promoting or progression pathways, via the following resources: Embase, MEDLINE, Cochrane and PubMed. The search terms used were physical activity, exercise, cancer and biological changes. We also scrutinised the references within the landmark papers published on this subject to ensure we did not miss any relevant papers. We found 222 unique clinical published papers and listed them according to the Preferred reporting items for systematic reviews and meta-analyses systemic review guidance.²⁷ Three authors independently assessed their appropriateness for inclusion in this review according to guidelines suggested by Sanderson *et al*²⁸ and excluded studies with inappropriate selection of participants; inappropriate measurement of variables and controls or where not written in English. In addition, we included the most relevant laboratory studies, which had the highest scientific relevance to this review which included 168 papers in total. For ease of explanation, these have been split into direct and indirect separate pathways but there is considerable overlap between them.

Direct anticancer pathways

An array of direct biological, epigenetic, metabolic and inflammatory changes occur in the body after exercise, acutely and over time.^{29 30} It is not yet, however, established which one, or combination of these, has the most significant influence on cancer pathways. The most notable candidate mechanisms are summarised here, in no particular order of importance.

To cite: Thomas RJ, Kenfield SA, Jimenez A. *Br J Sports Med* Published Online First: [please include Day Month Year] doi:10.1136/bjsports-2016-096343

Insulin-like growth factor (IGF-1) and its binding proteins, insulin-like growth factor-binding proteins (IGFBPs), have a central role in the regulation of cell growth. After binding to its receptor tyrosine kinase, IGF-1 activates several signalling pathways, leading to the inhibition of apoptosis, the promotion of cell growth and angiogenesis.^{31–33} Higher levels of IGF-1 would therefore be expected to increase tumour growth, and have been reported to be associated with a greater cancer risk.^{34–35} An inverse relationship is reported with IGFBP3 levels although this effect has not been confirmed in all studies.³⁶ Exercise has been shown to increase the levels of IGFBP3 and lower IGF-1, and in a large prospective cohort study of 41 528 participants, this was associated with a 48% reduction of cancer-specific deaths.²⁹ Decreased levels of IGF-1 in physically active patients have also been linked to an improved survival.³⁷

Epigenetic effects on gene expression, DNA repair and telomere length: Exercise can influence the phenotype expression of inherited genes via epigenetic biochemical alterations to chromosomes, such as histone modifications, DNA methylation, expression of microRNAs (miRNAs) and changes of the chromatin structure.^{38–39} Which of these epigenetic changes that have the most influence on cancer remains uncertain.^{38–39} A prospective pilot trial involving men with low-risk prostate cancer found a set of RAS family oncogenes (*RAN*, *RAB14* and *RAB8A*) to be downregulated after a healthy exercise and lifestyle programme.⁴⁰ In the prostate, RAN (ras-related nuclear protein) may function as an androgen receptor coactivator, and its expression is increased in tumour tissues.⁴⁰ Another study involving men on active surveillance, showed that 184 genes were differentially expressed between individuals who engaged in vigorous activity compared with sedentary individuals. Genes particularly sensitive to exercise included those involved in signalling cell cycling and those supporting DNA repair including BRCA1 and BRCA2 via histone deacetylase and miRNA pathways.^{41–42} The same upregulation of BRCA expression following exercise has been demonstrated in the rat mammary gland and clinically in women who were BRCA1 or BRCA2 mutation carriers.^{43–44} Markers of an improved cellular repair process were also reported in a study,⁴⁵ which showed that exercise upregulated the key regulator gene p53 and by doing so, encourages damaged cells to repair or if not possible, self-destruct.^{43–45}

Telomeres, the sequences of nucleotides at the end of the chromosomes that protect their integrity, are shortened with each cell division, so telomere length correlates with biological age.³⁹ Exercise has epigenetic effects on the telomere as well, which help to prevent its deregulation by protecting it from transcription errors caused by transcription of non-coding RNA, which occur during cell division.³⁹ In a clinical study involving men with early prostate cancer, those regularly exercising and eating healthily had longer telomeres and reduced prostate-specific antigen progression compared with sedentary controls with less healthy diets.⁴⁶

Vasoactive intestinal peptide (VIP) is a neuropeptide that increases proliferation, survival, androgen resistance and de-differentiation in human breast and prostate cancer cells lines.^{47–49} Serum VIP has been shown to transiently increase after acute exercise.^{49–50} For example, in an experiment involving 30 min of bicycle riding, increased levels were detected for ~20 min, although the rise was higher if the individual was sleep-deprived and lower if adequate glucose levels were maintained.⁵¹ This transient rise leads to the production of natural anti-VIP antibodies which explains the observation that individuals who regularly exercise have lower VIP titres.⁵² Patients with breast and prostate cancer have been found to have higher

VIP titres compared with matched pairs in the general population without cancer.^{52–53}

Oxidative stress and antioxidant pathways: Exercise, particularly if strenuous, produces reactive oxidative species (ROS) that, if significant, increases oxidative stress on DNA, which could potentially contribute to the initiation and progression of cancer.^{54–55} In response to this transient increase in ROS, especially after regular training, an adaptive upregulation of antioxidant genes occurs which results in greater production of antioxidant enzymes such as superoxide dismutase, glutathione and catalase.^{56–58} In a pilot study at the University of California, men who participated in ≥3 hours/week of vigorous physical activity had greater expression of the nuclear factor erythroid 2-related factor 2 (Nrf-2) in their normal prostate tissue compared with men who did less physical activity. The Nrf-2 protein stimulates the production of antioxidant enzymes and activation of other protective genes.⁴¹ Other studies have confirmed that trained individuals also have greater levels of antioxidant enzymes which would potentially increase their defence against environmental and ingested oxidising carcinogens.^{55–57–59–60} If nutritional deficiencies exist to impair the production of antioxidant enzymes or strenuous exercisers are elderly, where this adaptive process is known to be slower, there is a danger that strenuous exercise could do more harm than good.^{57–60} It is important, therefore, that attention is given to nutritionally healthy polyphenol-rich foods that enhance upregulation of antioxidant enzymes.^{9–56–57–59–60}

Heat shock proteins (HSPs) are produced in tissues, in response to a wide variety of physiological and environmental insults including infection, hypoxia, hyperthermia, dexamethasone and chemotherapy.^{61–62} They have cytoprotective functions including blocking apoptosis and allowing the cell to survive potentially lethal events; hence, they are substantially overexpressed following a myocardial infarction.⁵⁶ They are also increased acutely following a bout of exercise.^{56–61–63} This acute rise in HSP is significantly lower in trained athletes and is most pronounced after severe anaerobic exercise, especially if the participant is previously unfit.^{56–61–63} An increase in HSP is the hypothesised mechanism for exercise in protecting the heart in numerous animal studies and clinically in women with breast cancer receiving adjuvant anthracycline-based chemotherapy regimens who are physically active.^{61–64–65} An increase in HSP is also the suggested mechanism for exercise in reducing cognitive impairment during chemotherapy, by protecting the astrocytes and supportive cells within the brain.⁶⁶

There is a potential downside to this adaptive pathway, as cancer cells have learnt to harness the antiapoptotic properties of HSP, and hence HSP are markedly overexpressed in several cancer types.⁶³ Some cancers have even become HSP-dependent for their survival, which makes them an interesting potential therapeutic target.⁶⁷ Whether exercise increases HSP to a clinically meaningful level to protect cancer cells is not yet known, although the addition of very high levels of HSP to cell lines in one laboratory experiment did increase resistance to anthracyclines.⁶⁸ As cancer cells produce their own HSP in high quantities, it is unlikely that the changes in serum HSP after exercise have any influence on intratumoural levels.⁶⁵ This is supported by a recent experiment in mice that reported a better cancer response to adriamycin with concomitant exercise.⁶⁴ Nevertheless, further research is needed in humans to confirm whether it is appropriate to advise patients, who are unaccustomed to rigorous activities, to perform anaerobic exercise just before or immediately after chemotherapy.⁶⁹

Testosterone: High levels of androgens are associated with a higher incidence of prostate cancer,⁷⁰ but what happens to testosterone after exercise is complex and depends on the underlying level of fitness, exercise intensity and even mood at the time of training.⁷¹ It is widely stated that serum testosterone increases immediately after vigorous exercise,⁷¹⁻⁷³ but this has not been confirmed in all studies.⁷⁴⁻⁷⁵ This effect also appears to be very short-lived, around 15 min to an hour after exercise with levels returning to pre-exercise levels by 2 hours.⁷²⁻⁷⁶⁻⁷⁷ It is also often quoted that resistance training increases testosterone more than endurance exercises but there is very little to substantiate this in the literature. In fact, endurance exercise and resistance training have been reported to cause a transient increase in testosterone levels in men and women in a number of studies.⁷¹⁻⁷³⁻⁷⁶ It is important to note that these studies report that testosterone-binding protein also rises with exercise so the free, biologically active, testosterone proportion changes little.⁷⁸ Furthermore, this transient testosterone rise has not been reported in men over 55 years, when men are at increased risk of prostate cancer.⁷⁴⁻⁷⁵ More importantly, over time, regular moderate or intense exercise actually lowers testosterone as well as luteinising hormone and follicle-stimulating hormone due to a negative feedback mechanism and this can be a symptomatic issue for trained athletes.⁷¹⁻⁷²⁻⁷⁹⁻⁸⁰ This effect has been observed clinically following 30-day, 12-week and 12-month programmes.⁷¹⁻⁷³⁻⁷⁹⁻⁸¹ There are some studies reporting that a healthy lifestyle, including exercise, delayed the natural age-related decline in testosterone but this was only linked to obesity, metabolic syndrome, diabetes and dyslipidaemia, which causes testosterone deficiency.⁸² Current studies are inconclusive as to whether exercise further lowers serum androgen levels in men already taking androgen deprivation therapy (ADT),⁸³ although this is further complicated by inadequate methods for measuring testosterone levels in very low ranges.⁸⁴

Irisin is a type I trans-membrane messenger protein, which is produced in muscle cells in response to exercise.⁸⁵ One study reported that higher levels were linked to more favourable breast cancer prognostic risk at diagnosis.⁸⁶ In laboratory studies, irisin significantly reduced cancer cell proliferation, migration and viability in malignant cancer cell lines, without affecting non-malignant cells.⁸⁷ In another study, irisin enhanced the cytotoxic effect of the chemotherapy agent, doxorubicin, when added to malignant breast cells, which again was not observed in non-malignant cells.⁸⁷ This reduction in malignant potential of irisin, however, was not observed with colon, thyroid and oesophageal cancer cell lines.⁸⁸ Furthermore, reports questioned the existence of circulating human irisin as it was felt that human irisin antibodies used in commercial ELISA kits lacked required specificity.⁸⁹ However, a recent experiment used tandem mass spectrometry to compare irisin levels between sedentary participants and those following aerobic interval training, so the antibody shortcomings were circumvented, and they found a significant difference.⁹⁰

Immunity: During exercise, increased levels of catecholamines stimulate the recruitment of leucocytes into the peripheral blood, resulting in increased concentrations of neutrophils, lymphocytes and monocytes, including natural killer (NK)-cells, CD4+ T cells and B cells, and potentially improve immune surveillance against cancer.⁹¹⁻⁹² On the other hand, if exercise is too strenuous for that individual, it is followed by decreased concentrations of lymphocytes and impaired cellular-mediated immunity.⁹³ As a consequence, in another study there was an increase in risk of an infection in the weeks following a competitive ultra-endurance running event.⁹⁴ Following moderate

exercise regimes, however, particularly with regular training, most long-term studies suggest exercise improves immune function in all age groups.⁹¹⁻⁹² Its benefits are particularly clinically relevant in the elderly whose immune function is becoming less efficient,⁹⁵⁻⁹⁶ or obese individuals whose NK-cell numbers in blood and in solid organs, together with their cytotoxicity and cytokine secretion, are reduced.⁹⁷ This also implies a benefit for individuals with impaired immunity after cancer treatments, but these studies have yet to be conducted.⁵⁸

Chronic inflammation and prostaglandins: Although an inflammatory response is an important part of a healthy innate immunity, persistent low-grade increased chronic inflammatory activity is associated with age-related diseases such as Alzheimer's disease and atherosclerosis.⁹⁸⁻⁹⁹ Higher levels of inflammatory markers have also been found to be associated with cancer incidence, more advanced cancers at presentation and an increased risk of cancer-specific mortality.⁹⁹⁻¹⁰² Markers of chronic inflammation are higher among individuals who are overweight, sedentary, those with poor diets, type II diabetes and the elderly.⁹⁶⁻¹⁰³ One reason for this stems from overcompensation of an ailing immune system trying to maintain immunosenescence.⁹³⁻⁹⁵⁻⁹⁶ In these groups, poor interleukin (IL)-2 production leads to a decreased cytotoxic capacity of NK and T lymphocytes on a 'per cell' basis. To compensate for this, higher levels of inflammatory biomarkers such as C reactive protein, tumour necrosis factor (TNF), IL-6, cytokine antagonists and acute phase proteins are produced which increase concentrations of NK cells and T cells.⁹³⁻⁹⁵⁻⁹⁶⁻¹⁰³⁻¹⁰⁴ Exercise is known to enhance NK cell activity and increase T-cell production reducing the need for the immune system to compensate by increasing circulating inflammatory biomarkers.⁸³⁻⁹¹⁻⁹²⁻¹⁰⁵

Another reported mechanism concerns a mediator in the inflammatory pathway called apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC).³⁸⁻⁴⁵ ASC activates procaspase-1, which in turn activates the release of ILs and other inflammatory cytokines including TNF. The transcription status of the ASC gene is influenced by the epigenetic factors mentioned above, particularly methylation. Regular exercise upregulates the methylation of ASC, resulting in decreased activity of the gene in human monocytes.³⁹

Prostaglandins, which are biologically active lipids generated from arachidonic acid via the enzyme cyclo-oxidase (COX), also have an influence on chronic inflammation and carcinogenesis. The COX-1 enzymes are present in normal tissues and upregulate in response to trauma, infection or chemical injury, increasing prostaglandins, which in turn triggers an appropriate inflammatory cascade as part of a healthy immune response. COX-2 is also induced by cytokine growth factors but has higher expression in many tumours.¹⁰⁶ Chronically increased overproduction of prostaglandins, generated via COX-2, has been implicated in cancer progression, apoptosis, invasion, angiogenesis and metastases.¹⁰⁷⁻¹⁰⁸ Anti-inflammatory drugs and salicylates found in painkillers and fresh vegetables¹⁰⁸ have been shown to reduce COX-2 activation of prostaglandins which could explain their reported anticancer properties.¹⁰⁹⁻¹¹¹ Moderate, regular and non-traumatic exercise also reduces serum prostaglandin levels.¹¹²⁻¹¹³ For example, a study involving biopsies of rectal mucosa showed that leisure-time physical activity was inversely associated with prostaglandin-2 concentration (PGE₂). Overweight individuals (BMI > 25 kg/m²) also had increased mucosal concentrations. Most importantly, an increase in activity level from 5.2 to 27.7 MET-hours per week was associated with a 28% decrease in mucosal PGE₂ even before weight loss.¹¹⁴ This was confirmed in another study from Italy; subjects

Table 1 Mainly direct biochemical changes related to exercise

Class of effect	Effector molecule or gene	Effect of exercise on effector molecule or gene
Cell growth regulators	IGF-1 IGFBP3	Decreased levels ^{32–36} Increased levels ^{35 36}
Proteins involved in DNA damage repair	BRCA1 BRCA2	Increased expression ^{41–44} Increased expression ^{41–44}
Androgen receptor coactivators	RAS family oncogenes	Suppressed activity ⁴⁰
Regulators of apoptosis and cell cycle arrest	P53 Heat shock proteins	Enhanced activity ^{43–45} Enhanced activity ^{55 61–66}
Hormonal systems	Oestrogen Testosterone VIP Leptin Irisin Resistin	Reduced activity ^{29 70 117 125–143} Transient rise then reduced activity ^{70–84} Transient rise then reduced activity ^{49 51–53} Reduced activity ^{133 138–142 144} Enhanced activity ^{85–90} Reduced activity ^{123 124 145}
Immune system components	Natural killer cells White cells	Enhanced activity ^{91–97} Enhanced activity ^{91–94}
Inflammation	C reactive protein, interleukin-6, TNF α Prostaglandins COX-2	Reduced activity ^{93–102} Reduced activity ^{106–114} Reduced activity ^{106–114}
Oxidative stress and antioxidant pathways	Glutathione, catalase and superoxide dismutase	Increased activity ^{55 57 59 60}

COX-2, cyclo-oxidase-2; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; TNF, tumour necrosis factor; VIP, vasoactive intestinal peptide.

with type 2 diabetes and the metabolic syndrome, which showed that the anti-inflammatory effects of exercise were independent of achieving weight loss.¹¹⁵

Energy metabolism and insulin resistance: It has long been established that exercise reduces plasma insulin levels leading to increased insulin sensitivity in volunteers and athletes, but more recently this biochemical response has been reported in exercise intervention studies involving breast cancer survivors.^{116 117} Likewise, a number of RCTs have shown that exercise improves insulin sensitivity and glucose metabolism even in men receiving ADT, who have a significant risk of metabolic syndrome,^{118 119} including adiposity and increased lipids and sarcopenia.^{120 121} Hyperglycaemia and hyperinsulinaemia secondary to insulin resistance are associated with an increased risk of cancer, poorer prognostic features at presentation, higher risk of relapse after initial treatments and more rapid progression in men with castration-resistant prostate cancer.^{32 99 117 120 122} In addition, high levels of C peptide, a marker of insulin secretion, are associated with a more than twofold increased risk of prostate cancer-specific mortality.³⁶ One contributory factor for these worse outcomes may be resistin, also known as adipose tissue-specific secretory factor, which is a cysteine-rich adipose-derived peptide hormone that increases with insulin resistance through AMP kinase downregulation. Resistin is known to upregulate proinflammatory cytokines, which act via the nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) pathway to increase transcription of proteins involved in cell proliferation, inflammation and antiapoptosis.^{123 124}

Indirect anticancer pathways

Several non-direct factors contribute to anticancer biochemical benefits of exercise. As displayed in tables 1 and 2, there is overlap between direct effects of exercise and indirect effects gained from weight reduction particularly via leptin, adiponectin oestrogen and inflammatory markers but for clarity they have also been included in this section along with improvements in serum lipids, sunlight exposure and elevated mood:

Obesity, oestrogen, leptin and the effects of weight reduction: The neuropeptide cytokine leptin and sex hormone oestrogen

are generated in fat cells, so overweight, particularly postmenopausal women, have higher endogenous levels.^{125 144} Leptin is known to promote breast cancer directly and independently, as well as through involvement with the oestrogen and insulin signalling pathways, via enhanced angiogenesis and cell proliferation,¹⁶⁴ which explains the links between higher levels of leptin, adiposity and hormone-related cancers such as breast, prostate and ovary cancer.^{29 70 117 126–128 144} Conversely, serum concentration of another adipokine cytokine, adiponectin, is inversely correlated with adiposity, breast and prostate cancer risk most likely because it has anti-inflammatory properties.^{129–131} Furthermore, adiponectin also suppresses inactivation of nitric oxide which dose-dependently diminishes an increased tendency of tumour cell-induced platelet aggregation.¹³² Tumour cell-induced platelet aggregation increases metastatic potential by 'cloaking' tumour cells with adherent platelets, protecting them from NK-cell-mediated killing.¹³³

A number of studies have shown that exercise programmes help individuals to lose weight^{16 134–136} and some of these demonstrated that weight reduction resulted in lower serum sex hormones and leptin levels.¹³⁷ It is unlikely, however, that a reduction in adiposity is a major anticancer mechanism because exercise programmes, at best, only usually show a modest

Table 2 Mainly indirect biological benefits of exercise

Associated activity	Effector molecule or pathway	Effect
Sunlight exposure	Vitamin D Circadian rhythm	Higher ^{146–151} Improved ^{152 153}
Weight loss	Oestrogen Leptin Insulin resistance Triglycerides/cholesterol Adiponectin Platelets	Lower ^{29 70 117 125–143} Lower ^{133 138–142} Greater ^{32 116–120 122} Lower ^{154–156} Higher ^{129–132} Reduces aggregation ^{132 133}
Mood	Endorphins Monoamines	Increased release ^{157–161} Higher levels ^{162 163}

reduction in weight.^{136 138–140} Furthermore, there is evidence that even before weight reduction occurs, exercise directly lowers serum oestrogen and leptin levels and raises adiponectin levels independent of weight loss.^{137 139 141 142} In one clinical study, this was quantified as every 100 min of exercise giving a 3.6% lowering of serum oestrogen.¹⁴³

Exercise and dietary modification help weight control and lower serum triglycerides, total cholesterol, and improve the ratio of high density lipoprotein to low density lipoprotein.¹⁴³ Epidemiological studies have suggested that high levels of cholesterol in the blood are associated with increased risk of cancer and progression of cancer.^{154–156}

Vitamin D levels and sunlight exposure: These are both higher among those who exercise outdoors regularly¹⁴⁶ as UV-B radiation's interaction with the skin produces most of the body's required vitamin D. Excess sunlight, particularly associated with sunburn, is the main cause of epithelial skin damage, premature ageing and skin cancers and clearly should be avoided. On the other hand, regular sensible sun exposure has an anticancer property by maintaining adequate serum vitamin D levels.¹⁴⁶ The mechanism by which vitamin D influences the incidence and progression of cancer is thought to be due to calcitriol's effect on cellular proliferation, differentiation and apoptosis.^{147–149} The vitamin D receptor is highly expressed in epithelial cells known to be at risk of carcinogenesis, such as the breast, skin and prostate.¹²⁵ Higher vitamin D levels are associated with lower colorectal, breast and prostate cancer mortality.^{150 151 165–168}

Despite this, a direct causal link has not been established nor has any benefit of correcting vitamin D levels with supplementation; important limitations regarding the dose, adherence and induction period could explain these findings.¹⁵¹ Sunlight exposure, independent of vitamin D levels, has been linked to a lower incidence of prostate cancer.¹⁵² It has been postulated that the benefit of sunlight exposure may be mediated through vitamin D and other pathways and mechanisms such as modulation of the immune system and the circadian rhythm.¹⁵³

Psychological well-being: As well as being distressing, anxiety and depression have been linked to reduced survival following radical cancer treatments.^{62 157} Of note, a large prospective cohort study from California reported that 4.6% of 41 000 men, who were clinically depressed after prostate cancer diagnosis, had a 25% reduction in disease-specific survival compared with non-depressed men.¹⁵⁸ Another trial involving individuals from Korea with head and neck cancer reported similar findings.¹⁴⁵ Regular exercise, especially if in groups and combined with relaxation, mindfulness and healthy eating programmes have been shown to help alleviate mood, and reduce anxiety and fear of relapse.^{25 159–162} The mechanism by which exercise helps fight depression has not yet been firmly established but hypotheses include increased endorphin and monoamine release, mental distraction, rises in core temperatures and better compliance to medical interventions.^{145 158 159} In addition, light exposure, which increases with outdoor exercise, has been linked to a reduction in non-seasonal depressive disorders.¹⁶³

In conclusion, clinical studies suggest a significant benefit for regular exercise after cancer for improving well-being and disease outcomes.³⁰ The most feasible biochemical pathways, supporting a direct and indirect anticancer mechanism of action, have been summarised in this article but there are likely to be others yet to be reported. It also remains unclear which of these mechanism has the most important role, or whether they vary by person or by disease. Although they have been subclassified, for ease of explanation in this article, they are clearly inter-related, especially

the inflammation, immunity and insulin resistance pathways. In the UK, despite these benefits, which are being highlighted by patient advocacy groups and charities, levels of exercise after cancer remain poor,¹⁶⁹ while funding for a national exercise programme has been hampered by the shortage of RCTs. Given the magnitude of the potential benefits of exercise, more multicentre RCTs evaluating disease outcomes, combined with biochemical determinants, are clearly needed. The forthcoming INTERVAL and PANTERA studies and ongoing CHALLENGE study are most welcomed.

What are the findings?

- ▶ This is a comprehensive and up-to-date understanding of the biological effects of exercise which may affect cancer.
- ▶ This review highlights the shortfalls in knowledge and understanding of exercise biochemistry.
- ▶ An investigation of the biological processes which may affect cancer.

How might it impact on clinical practice in the near future?

- ▶ Provide a detailed understanding of cancer and exercise, essential for clinical trial development.
- ▶ A useful summary of the effects of exercise for exercise scientists and oncologists interested in cancer rehabilitation.
- ▶ This summary provides the biological evidence to help motivate patients into exercise programmes.

Twitter Follow Robert Thomas @#cancernetuk

Contributors RJT was the main researcher, data collector and writer of this review paper. Substantial additions and editing was made by SAK, with minor editing by AJ.

Competing interests None declared.

Ethics approval Ethics Committee/Institutional Review Board approval has not been obtained, as this study does not involve human subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no additional data for this scientific review relevant to data sharing.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

- 1 Voskuil DW, Monnikhof EM, Elias SG, *et al*. Task force physical activity and cancer. Physical activity and endometrial cancer risk, a systematic review of current evidence. *Cancer Epidemiol Biomarkers Prev* 2007;16:639–48.
- 2 Boyle T, Keegel T, Bull F, *et al*. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *J Natl Cancer Inst* 2012;104:1548–61.
- 3 Keimling M, Behrens G, Schmid D, *et al*. The association between physical activity and bladder cancer: a systematic review and meta-analysis. *Br J Cancer* 2014;110:1862–70.
- 4 Behrens G, Leitzmann MF. The association between physical activity and renal cancer: systematic review and meta-analysis. *Br J Cancer* 2013;108:798–811.
- 5 Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat* 2013;137:869–82.

- 6 Kenfield S, Batista J, Jahn JL, *et al.* Development and application of a lifestyle score for prevention of lethal prostate cancer. *J Natl Cancer Inst* 2016;108:djv329.
- 7 Tardon A, Lee WJ, Delgado-rodriguez M, *et al.* Leisure-time physical activity and lung cancer: a meta-analysis. *Cancer Causes Control* 2005;16:389–97.
- 8 Thune I, Brenn T, Lund E, *et al.* Physical activity and the risk of breast cancer. *N Engl J Med* 1997;336:1269–75.
- 9 Tomlinson D, Diorio C, Beyene J, *et al.* Effect of exercise on cancer-related fatigue: a meta-analysis. *Am J Med Rehabil* 2014;93:675–86.
- 10 Mishra SI, Scherer RW, Snyder C, *et al.* Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012;(8):CD008465.
- 11 Gerritsen J, Vincent A. Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomized controlled trials. *Brit J Sport Med* 2016;50:796–803.
- 12 Fong DYT, Ho JWT, Hui BPH, *et al.* Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *Br Med J* 2012;344:e70.
- 13 Markes M, Brockow T, Resch K. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev* 2006;(4):CD005001.
- 14 McNeely M, Campbell K, Rowe B, *et al.* Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *Can Med Assoc J* 2006;175:34–41.
- 15 Holmes MD, Chen WY, Feskanich D, *et al.* Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;293:2479–86.
- 16 Irwin ML, Alvarez-Reeves M, Cadmus L. Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. *Obesity (Silver Spring)* 2009;17:1534–41.
- 17 Meyerhardt JA, Heseltine D, Niedzwiecki D, *et al.* Impact of physical activity on patients with stage III colon cancer: findings from intergroup trial CALGB 89803. *J Clin Oncol* 2006;24:3535–341.
- 18 Meyerhardt JA, Sato K, Niedzwiecki D. Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Natl Cancer Inst* 2012;104:1702–11.
- 19 Kenfield S, Stampfer M, Giovannucci E, *et al.* Physical activity and survival after prostate cancer diagnosis in the Health Professionals Follow Up study. *J Clin Oncol* 2011;29:726–32.
- 20 Spencer E, Appleby P, Davey G, *et al.* Diet and body mass index in 38 000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes* 2003;27:728–34.
- 21 Ballard-Barbash R, Friedenreich CM, Courneya KS, *et al.* Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104:815–40.
- 22 Richman EL, Kenfield SA, Stampfer MJ, *et al.* Physical activity and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer Res* 2011;71:1–7.
- 23 Friedenreich CM, Wang Q, Neilson HK, *et al.* Physical activity and survival after prostate cancer. *Eur Urol* 2016;15:1241–5.
- 24 Bonn SE, Sjölander A, Lagerros YT, *et al.* Physical activity and survival among men diagnosed with prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2015;24:57–64.
- 25 Courneya KS, Booth C, Gill S, *et al.* The colon health and life-long exercise change trial: a randomized trial of The National Cancer Institute of Canada Clinical Trials Group. *Curr Oncol* 2008;15:271–8.
- 26 Saad F, Kenfield S, Chan J, *et al.* Intense exercise for survival among men with castration resistant metastatic prostate cancer (INTERVAL—MRCPC): A Movement funded multicenter randomized controlled phase III Trial. *Abstract ASCO JCO* 2016 #163966
- 27 Moher D, Liberati A, Tetzlaff J, *et al.* The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
- 28 Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007;36:666–76.
- 29 Haydon AM, Macinnis RJ, English DR, *et al.* The effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut* 2006;55:62–7.
- 30 Thomas R, Holm M. The benefits of exercise after cancer—an international review of the clinical and microbiological benefits. *Br J Med Pract* 2014;1:2–9.
- 31 Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst* 2000;92:1472–89.
- 32 Lubik AA, Gunter JH, Hollier BG, *et al.* IGF2 increases de novo steroidogenesis in prostate cancer cells. *Endocr Relat Cancer* 2013;20:173–86.
- 33 Freier S, Weiss O, Eran M, *et al.* Expression of the insulin-like growth factors and their receptors in adenocarcinoma of the colon. *Gut* 1999;44:704–8.
- 34 Palmqvist R, Hallmans G, Rinaldi S, *et al.* Plasma insulin-like growth factor, insulin-like growth factor binding protein, and colorectal cancer: a prospective study in northern Sweden. *Gut* 2002;50:642–6.
- 35 Ryan CJ, Haqq CM, Simko J, *et al.* Expression of insulin-like growth factor-1 receptor in local and metastatic prostate cancer. *Urol Oncol* 2007;25:134–40.
- 36 Ma J, Pollak MN, Giovannucci E, *et al.* Prospective study of colorectal cancer risk in men and plasma levels of Insulin like growth factor (IGF)-1 and IGF binding protein-3. *J Natl Cancer Inst* 1999;91:620–5.
- 37 Irwin ML, Smith AW, McTiernan A, *et al.* Influence of physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. *J Clin Oncol* 2008;26:3958–64.
- 38 Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *J Nutr* 2002;132:3456S–64S.
- 39 Ntanasios-stathopoulos J, Tzanninis J, Philipou A, *et al.* Epigenetic regulation of gene expression induced by exercise. *J Musculoskeletal Neurol Interact* 2013;13:133–46.
- 40 Ornish D, Magbanua MJ, Weider G, *et al.* Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci USA* 2008;105:8369–74.
- 41 Magbanua MJ, Richman EL, Sosa EV, *et al.* Physical activity and prostate gene expression in men with low-risk prostate cancer. *Cancer Causes Control* 2014;25:515–23.
- 42 Tuma RS. How exercise increases BRCA1/2 expression in normal tissue of prostate cancer. *Oncology Times UK* 2012;9:10–12.
- 43 Wang M, Yu B, Westerlind K, *et al.* Prepubertal physical activity up-regulates estrogen receptor beta, BRCA1 and p53 mRNA expression in the rat mammary gland. *Breast Cancer Res Treat* 2009;115:213–20.
- 44 Pijpe A, Manders P, Brohet RM, *et al.* Physical activity and the risk of breast cancer in BRCA1/2 mutation carriers. *Breast Cancer Res Treat* 2010;120:235–44.
- 45 Sharafi H, Rahimi R. The effect of resistance exercise on p53, caspase-9, and caspase-3 in trained and untrained men. *J Strength & Cond Res* 2012;26:1142–8.
- 46 Ornish D, Lin J, Chan JM, *et al.* Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol* 2013;14:1112–20.
- 47 Valdehita A, Bajo AM, Fernández-Martínez AB, *et al.* Nuclear localization of vasoactive intestinal peptide (VIP) receptors in human breast cancer. *Peptides* 2010;31:2035–45.
- 48 Power RF, Bishop AE, Wharton J, *et al.* Vasoactive intestinal peptide and related Peptides. *Ann N Y Acad Sci* 1988;527:314–25.
- 49 Xie Y, Wolff DW, Lin MF, *et al.* Vasoactive intestinal peptide transactivates the androgen receptor through a protein kinase A-dependent extracellular signal-regulated kinase pathway in prostate cancer LNCaP cells. *Mol Pharmacol* 2007;72:73–85.
- 50 Collado B, Carmena MJ, Sánchez-Chapado M, *et al.* Expression of vasoactive intestinal peptide and functional VIP receptors in human prostate cancer: antagonistic action of a growth-hormone-releasing hormone analog. *Int J Oncol* 2005;26:1629–35.
- 51 Opstad PK. The plasma vasoactive intestinal peptide (VIP) response to exercise is increased after prolonged strain, sleep and energy deficiency and extinguished by glucose infusion. *Peptides* 1987;8:175–8.
- 52 Veljkovic M, Branch DR, Dopsaj V, *et al.* Can Natural Antibodies to VIP facilitate which increase with exercise, help prevention and supportive treatment of breast Cancer? *Med Hypothesis* 2011;77:404–8.
- 53 Collado B, Carmena M, Sánchez-Chapado M, *et al.* Expression of vasoactive intestinal peptide and functional VIP receptors in human prostate cancer: antagonistic action of a growth-hormone-releasing hormone analogue. *Int J Oncol* 2005;26:1629–35.
- 54 Gupta-Elera G, Garrett AR, Robison RA, *et al.* The role of oxidative stress in prostate cancer. *Eur J Cancer Prev* 2012;21:155–62.
- 55 Niess AM, Dickhuth HH, Northoff H, *et al.* Free radicals and oxidative stress in exercise—immunological aspects. *Exerc Immunol Rev* 1999;5:22–56.
- 56 Fehrenbach E, Northoff H. Free radicals, exercise, apoptosis and heat shock proteins. *Exerc Immunol Rev* 2001;7:66–89.
- 57 Kojda G, Hambrecht R. Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective antioxidant therapy? *Cardiovasc Res* 2005;67:187–97.
- 58 Mackinnon LT. Current challenges and future expectations in exercise immunology: back to the future. *Med Sci Sports Exerc* 1994;26:191–4.
- 59 Gomez-Cabrera MC, Domenech E, Viña J. Moderate exercise is an antioxidant: up regulation of antioxidant genes by training. *Free Radic Biol Med* 2008;44:126–31.
- 60 Ji LL. Exercise at old age: does it increase or alleviate oxidative stress? *Ann NY Acad Sci* 2001;928:236–47.
- 61 Lanchester GI. Exercise induces the release of heat shock protein 72 from the human brain in vivo. *Stress Chaperones* 2004;9:276–80.
- 62 Powers SK, Locke AM, Demirel HA. Exercise, heat shock proteins and myocardial protection from I-R injury. *Med Sci Sports Exerc* 2001;33:386–92.
- 63 Ciocc DR, Calderwood SK. Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications. *Cell Stress Chaperone* 2005;10:86–103.
- 64 Kavazis AN, Smuder AJ, Min K, *et al.* Short-term exercise training protects against doxorubicin induced cardiac mitochondrial damage independent of HSP72. *Am J Physiol Heart Circ Physiol* 2010;299:H1515–24.

- 65 Scott JM. Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer—current evidence and underlying mechanisms. *Circulation* 2011;124:642–50.
- 66 Calabrese V, Scapagnini G, Colombrita C, et al. Redox regulation of heat shock protein expression in aging and neurodegenerative disorders associated with oxidative stress: a nutritional approach. *Amino acids* 2003;25:437–44.
- 67 Hahleh Z, Tfyali A, Najm A, et al. Heat shock proteins in cancer: targeting the 'chaperones'. *Future Med Chem* 2012;4:927–35.
- 68 Fuqua SAW, Oesterreich S, Hilsenbeck SG, et al. Heat Shock proteins and drug resistance. *Breast Cancer Res Treat* 1994;32:67–71.
- 69 Sturgeon K, Schadler K, Muthukumar G, et al. Concomitant low dose doxorubicin treatment and exercise. *Am J Physiol-Reg* 2014;307:685–92.
- 70 Kaaks R, Lukanova A. Effects of weight control and physical activity in cancer prevention: role of endogenous hormone metabolism. *Ann NY Acad Sci* 2002;963:268–81.
- 71 Hackney AC. Endurance exercise training and reproductive endocrine dysfunction in men: alterations in the hypothalamic-pituitary-testicular axis. *Curr Pharm Des* 2001;7:261–73.
- 72 Sgro P, Romanelli F, Felici F, et al. Testosterone responses to standardized short-term sub-maximal 30 mins and maximal endurance exercises 60 mins: issues on the dynamic adaptive role of the hypothalamic-pituitary-testicular axis. GH and testosterone transient rise. *J Endocrine Invest* 2014;37:13–24.
- 73 Enea C, Boisseau N, Ottavy M, et al. Effects of menstrual cycle, oral contraception and training on exercise-induced changes in circulating DHEA-sulphate and testosterone in young women. *Eur J Appl Physiol* 2009;106:365–73.
- 74 Niklas BJ, Ryan AJ, Treuth MM, et al. Testosterone, growth hormone and IGF-I responses to acute and chronic resistive exercise in men aged 55–70 years. *Int J Sports Med* 1995;16:445–50.
- 75 Craig BW, Brown R, Everhart J. Effects of progressive resistance training on growth hormone and testosterone levels in young and elderly subjects. *Mech Ageing Dev* 1989;49:159–69.
- 76 Jensen J, Oftebro H, Breigan B, et al. Comparison of changes in testosterone concentrations after strength and endurance exercise in well trained men. *Eur J Appl Physiol Occup Physiol* 1991;63:467–71.
- 77 Sutton JR, Coleman MJ, Casey J, et al. Androgen response during physical exercise. *BMJ* 1973;1:520–2.
- 78 Hayes LD. Six weeks of conditioning exercise increases total, but not free testosterone in lifelong sedentary aging men. *Ageing Male* 2015;18:195–200.
- 79 MacKellvie KJ, Taunton JE, McKay HA, et al. Bone mineral density and serum testosterone in chronically trained, high mileage 40–55-year-old male runners. *Br J Sports Med* 2000;34:273–8.
- 80 Hawkins VN, Foster-Schubert K, Chubak J, et al. Effect of exercise on serum sex hormones in men: a 12-month randomized clinical trial. *Med Sci Sports Exerc* 2008;40:223–33.
- 81 Safarinejad MR, Azma K, Kolahi AA. The effects of intensive, long-term treadmill running on reproductive hormones, hypothalamus-pituitary-testis axis and semen quality: a randomized controlled study. *J Endocrinol* 2009;200:259–71.
- 82 Haring R, Ittermann T, Vöelzke H, et al. Prevalence, incidence and risk factors of testosterone deficiency in a population-based cohort of men: results from the study of health Pomerania. *Ageing Male* 2010;13:247–57.
- 83 Zimmer P, Jäger E, Bloch W, et al. Influence of a six month endurance exercise program on the immune function of prostate cancer patients undergoing antiandrogen therapy or chemotherapy: design and rationale of the Prolmmun study. *BMC cancer* 2013;13:272.
- 84 Matsumoto AM, Bremner WJ. Serum testosterone assays-accuracy matters. *J Clin Endocrinol Metab* 2004;89:520–4.
- 85 Boström P, Wu J, Jedrychowski MP, et al. Irisin induces brown fat of white adipose tissue in vivo and protects against diet-induced obesity and diabetes. *Nature* 2012;481:463–8.
- 86 Provatopoulou X, Georgiou G, Kalogera E, et al. Serum irisin levels are lower in patients with breast cancer: association with diagnosis and disease tumour characteristics. *BioMed Central* 2015;15:898.
- 87 Gannon NP, Vaughan RA, Garcia-Smith R, et al. Effects of the exercise-inducible myokine irisin on malignant and non-malignant breast epithelial cell behavior in vitro. *Int J Cancer* 2015;115:136.
- 88 Moon HS, Mantzoros CS. Regulation of cell proliferation and malignant potential by irisin in endothelial, colon, thyroid and oesophageal cancer cell lines. *Metab Clin Exp* 2014;63:188–93.
- 89 Albrecht E, NORheim F, Thiede B, et al. Irisin—a myth rather than an exercise-inducible myokine. *Sci Rep* 2015;5:8889.
- 90 Jedrychowski MP, Wrann CD, Paulo JA, et al. Detection and quantitation of circulating human irisin by tandem mass spectrometry. *Cell Metab* 2015;22:734–40.
- 91 Wang JS, Weng TP. Hypoxic exercise training promotes antitumour cytotoxicity of natural killer cells in young men. *Clin Sci* 2011;121:343–53.
- 92 Radom-Aziz S, Zaldivar FP, Haddad F, et al. Impact of brief exercise on peripheral blood NK-cell gene and microRNA expression in young adults. *J Appl Physiol* 1985 (2013 online);114:628–36.
- 93 Hoffman-Goetz L, Pedersen BK. Exercise and the immune system: a model of the stress response? *Immunol Today* 1994;15:382–7.
- 94 Pedersen BK, Bruunsgaard H. How physical exercise influences the establishment of infections. *Sports Med* 1995;19:393–400.
- 95 Rukavina D, Laskarin G, Rubesa G, et al. Age-related decline of perforin expression in human cytotoxic T lymphocytes and natural killer cells. *Blood* 1998;92:2410–20.
- 96 Franceschi C, Monti D, Sansoni P, et al. The immunology of exceptional individuals: the lesson of centenarians. *Immunol Today* 1995;16:12–16.
- 97 Lautenbach A, Breitmeier D, Kuhlmann S, et al. Human obesity reduces the number of hepatic leptin receptor (Ob-R) expressing NK-cells. *Endocr Res* 2011;36:158–66.
- 98 Khansari N, Shakiba Y, Mahmoudi M, et al. Chronic inflammation and oxidative stress as a major cause of age-related diseases and cancer. *Recent Pat Inflamm Allergy Drug Discov* 2009;3:73–80.
- 99 Wolpin BM, Bao Y, Qian ZR. Hyperglycemia, insulin resistance, impaired pancreatic β -Cell function, and risk of pancreatic cancer. *Natl Cancer Inst* 2013;105:1027–35.
- 100 Stark JR, Li H, Kraft P, et al. Circulating pre-diagnostic interleukin-6 and C-reactive protein and prostate cancer incidence and mortality. *Int J Cancer* 2009;124:2683–9.
- 101 Ismail HA, Lessard L, Mes-Masson AM, et al. Expression of NF-kappaB in prostate cancer lymph node metastases. *Prostate* 2004;58:308–13.
- 102 Michalaki V, Syrigos K, Charles P, et al. Serum levels of IL-6 and TNF-alpha correlate with clinicopathological features and patient survival in patients with prostate cancer. *Br J Cancer* 2004;90:2312–16.
- 103 Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444:860–7.
- 104 Nijhuis J, Rensen SS, Slaats Y, et al. Neutrophil activation in morbid obesity, chronic activation of acute inflammation. *Obesity (Silver Spring)* 2009;17:2014–18.
- 105 Nicklas BJ, Hsu FC, Brinkley TJ, et al. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. *J Am Geriatr Soc* 2008;56:2045–52.
- 106 Madaan S, Abel PD, Chaudhary KS, et al. Cytoplasmic induction and over-expression of cyclooxygenase-2 in human prostate cancer: implications for prevention and treatment. *BJU Int* 2000;86:736–41.
- 107 Hsu AL, Ching TT, Wang DS, et al. The cyclooxygenases-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2. *J Biol Chem* 2000;275:11397–403.
- 108 Liu XH, Yao S, Kirschenbaum A, et al. NS398, a selective cyclooxygenase-2 inhibitor, induces apoptosis and down-regulates bcl-2 expression in LNCaP cells. *Cancer Res* 1998;58:4245–9.
- 109 Greenberg ER, Baron JA, Freeman DH JR, et al. Reduced risk of large-bowel adenomas among aspirin users. The Polyp Prevention Study Group. *J Nat Cancer Instit* 1993;85:912–16.
- 110 Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 1991;325:1593–6.
- 111 Harris RE, Namboodiri KK, Farrar WB. Non steroidal anti-inflammatory drugs and breast cancer. *Epidemiology* 1996;7:203–5.
- 112 Anderson SD, Pojer R, Smith ID, et al. Exercise-related changes in plasma levels of 15-keto-13,14-dihydro-prostaglandin F2alpha and noradrenaline in asthmatic and normal subjects. *Scand J Respir Dis* 1976;57:41–8.
- 113 Fairey AS, Courneya KS, Field CJ, et al. Physical exercise and immune system function in cancer survivors: a comprehensive review and future directions. *Cancer* 2002;94:539–51.
- 114 Martinez ME, Heddens D, Earnest DL. Physical activity, body mass index, and prostaglandin E₂ levels in rectal mucosa. *J Natl Cancer Inst* 1999;91:950–3.
- 115 Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis* 2010;20:608–17.
- 116 Ligibel L, Campbell A, Chen H, et al. Impact of physical activity on insulin levels in breast cancer survivors. *J Clin Oncol* 2007;26(6):907–12.
- 117 Irwin ML, Varma K, Alvarez-Reeves M, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale exercise and survivorship study. *Cancer Epidemiol Biomarkers Prev* 2009;18:306–13.
- 118 Segal R, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol* 2009;20:344–51.
- 119 Hvid T, Winding K, Rinnov A, et al. Endurance training improves insulin sensitivity and body composition in prostate cancer patients treated with androgen deprivation therapy. *Endocr Relat Cancer* 2013;20:621–32.
- 120 Flanagan J, Gray PK, Hahn N, et al. Presence of the metabolic syndrome is associated with shorter time to castration-resistant prostate cancer. *Ann Oncol* 2011;22:801–7.
- 121 Rhee H, Gunter JH, Heathcote P, et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. *BJU Int* 2015;115(Suppl 5):3–13.

- 122 Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer* 2007;121:856–62.
- 123 Koerner A, Kratzsch J, Kiess W, et al. Adipocytokines: leptin—the classical, resistin—the controversial, adiponectin—the promising, and more to come. *Best Pract Res Clin Endocrinol Metab* 2005;19:525–46.
- 124 Zimmerlin L, Donnenberg AD, Rubin JP, et al. Regenerative therapy and cancer: in vitro and in vivo studies of the interaction between adipose-derived stem cells and breast cancer cells from clinical isolates. *Tissue Eng Part A* 2011;17:93–106.
- 125 Hoffmann-Goetz L, Apter D, Demark-Wahnefried W, et al. Possible mechanisms mediating an association between physical activity and breast cancer. *Cancer* 1998;83(Suppl 3):S621–8.
- 126 Wu AH, Yu MC. Tea, hormone-related cancers and endogenous hormone levels. *Mol Nutr Food Res* 2006;50:160–9.
- 127 Folkert E, Dowset M. Influence of sex hormones on cancer progression. *J Clin Oncol* 2010;28:4034–44.
- 128 Niu J, Jiang L, Guo W, et al. The association between leptin level and breast cancer: a meta-analysis. *PLoS ONE* 2013;8:e67349.
- 129 Li H, Stampfer MJ, Mucci L, et al. A 25-year prospective study of plasma adiponectin and leptin concentrations and prostate cancer risk and survival. *Clin Chem* 2010;56:34–43.
- 130 Booth A, Magnuson A, Fouts J, et al. Adipose tissue, obesity and adipokines: role in cancer promotion. *Horm Mol Biol Clin Invest* 2015;21:57–74.
- 131 Kang JH, Yu BY, Youn DS, et al. Relationship of serum adiponectin and resistin levels with breast cancer risk. *J Korean Med Sci* 2007;22:117–21.
- 132 Restituto P, Colina I, Varo JJ, et al. Adiponectin diminishes platelet aggregation and sCD40L release. Potential role in the metabolic syndrome. *Am J Physiol Endocrinol Metab* 2010;298:E1072–7.
- 133 Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. *Nat Rev Cancer* 2011;11:123–34.
- 134 Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol* 2008;9:1039–47.
- 135 Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol* 2002;20:1128–43.
- 136 Rock CL, Flatt SW, Byers TE, et al. Results of the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial: a behavioral weight loss intervention in overweight or obese breast cancer survivors. *J Clin Oncol* 2015;33:3169–76.
- 137 Friedenreich CM, Woolcott CG, McTiernan A, et al. Alberta physical activity and postmenopausal breast cancer prevention trial: sex hormone changes. *J Clin Oncol* 2010;28:1458–66.
- 138 Foster-Schubert KE, Alfano CM, Duggan CR, et al. Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese post-menopausal women. *Obesity (Silver Spring)* 2012;20:1628–38.
- 139 Abbenhardt C, McTiernan A, Alfano CM, et al. Effects of individual and combined dietary weight loss and exercise interventions in postmenopausal women on adiponectin and leptin levels. *J Intern Med* 2013;274:163–75.
- 140 Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2015;4:e002014.
- 141 Kossman DA, Williams NI, Domcheck SM, et al. Exercise lowers estrogen and progesterone levels in premenopausal women at high risk of breast cancer. *J Appl Physiol* 2011;111:1687–93.
- 142 Kraemer RR, Chu H, Castracane VD. Leptin and exercise. *Exp Biol Med* 2002;227:701–8.
- 143 Schmitz KH, Williams NI, Kontos D, et al. Dose–response effects of aerobic exercise on estrogen among women at high risk for breast cancer: a randomized controlled trial. *Breast Cancer Res Treat*. 2015;154:309–18.
- 144 Surmacz E. Obesity hormone leptin; a new target for breast cancer? *Breast Cancer Res* 2007;9:301.
- 145 Kim HJ, Lee Y, Won E, et al. Expression of resistin in the prostate and its stimulatory effect on prostate cancer cell proliferation. *BJU Int* 2011;108:E77–83.
- 146 Chomistek AK, Chiuev SE, Jensen MK, et al. Vigorous physical activity, mediating biomarkers, and risk of myocardial infarction. *Med Sci Sports Exerc* 2011;43:1884–90.
- 147 Lazzeroni M, Serrano D, Pilz S, et al. Vitamin D supplementation and cancer: review of randomized controlled trials. *Anticancer Agents Med Chem* 2013;13:118–25.
- 148 Schwartz GG, Vitamin D, sunlight and the epidemiology of prostate cancer. *Anti-Cancer Agent Me* 2013;13:45–57.
- 149 Chiang KC, Chen TC. The anti-cancer actions of vitamin D. *Anticancer Agents Med Chem* 2013;13:126–39.
- 150 Zgaga L, Theodoratou E, Farrington S, et al. Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. *JCO* 2014;32:2430–9.
- 151 Ng K, Meyerhardt J, Wu K, et al. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. *J Clin Oncol* 2008;26:2984–91.
- 152 Luscombe CJ, French ME, Liu S, et al. Prostate cancer risk: associations with ultraviolet radiation, tyrosinase and melanocortin-1 receptor genotypes. *Breast Cancer Res Treat* 2001;85:1504–9.
- 153 van der Rhee H, Coebergh JW and de Vries D. Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. *Eur J Cancer* 2013;49:1422–36.
- 154 Stulb SC, McDonough JR, Greenberg BG, et al. The relationship of nutrient intake and exercise to serum cholesterol levels in white males in Evans County, Georgia. *Am J Clin Nutr* 1965;16:238–42.
- 155 Platz EA, Till C, Goodman PJ, et al. Men with low serum cholesterol have a lower risk of high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev* 2009;18:2807–13.
- 156 Platz EA, Clinton SK, Giovannucci E. Association between plasma cholesterol and prostate cancer in the PSA era. *Int J Cancer* 2008;123:1693–8.
- 157 Kadan-Lottick NS, Vanderwerker LC, Block SD, et al. Psychiatric disorders and mental health service use in patients with advanced cancer. *Cancer* 2005;104:2872–81.
- 158 Prasad SM, Eggen SE, Lipsitz SR, et al. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate cancer. *J Clin Oncol* 2014;32:2471–8.
- 159 Craft LL, Perna FM. The benefits of exercise for the clinically depressed prim care companion. *J Clin Psychiatry* 2004;6:104–11.
- 160 Reid-Arndt SA, Cox CR. Stress, coping and cognitive deficits in women after surgery for breast cancer. *J Clin Psychol Med Settings* 2012;19:127–37.
- 161 Pischke CR, Frensd S, Ornish D, et al. Lifestyle changes are related to reductions in depression in persons with elevated coronary risk factors. *Psychol Health* 2010;25:1077–100.
- 162 Rao M, Raghuram N, Nagendra H, et al. Anxiolytic effects of a yoga program in early breast cancer patients undergoing conventional treatment: a randomized controlled trial. *Complementary Ther Med* 2009;17:1–8.
- 163 Lam R, Levitt AJ, Levitan R, et al. Efficacy of bright light treatment, fluoxetine and the combination in patients with non-seasonal major depressive disorder: a randomized controlled trial. *JAMA Psychiatry* 2015;72:1021–8.
- 164 Schmidt S, Monk JM, Robinson LE, et al. The integrative role of leptin, oestrogen and the insulin family in obesity-associated breast cancer: potential effects of exercise. *Obes Rev* 2015;16:473–87.
- 165 Rose AA, Elser C, Ennis M, et al. Blood levels of vitamin D and early stage breast cancer prognosis: a systematic review and meta-analysis. *Br J Cancer* 2001;85:1504–9.
- 166 Mondul AM, Weinstein SJ, Moy KA, et al. Circulating 25-hydroxyvitamin d and prostate cancer survival. *Cancer Epidemiol Biomarkers Prev* 2016;25:665–69.
- 167 Pilz S, Kienreich K, Tomaschitz A, et al. Vitamin D and cancer mortality: systematic review of prospective epidemiological studies. *Anti-Cancer Agent Me* 2013;13:107–17.
- 168 Giovannucci E. Epidemiology of vitamin d and colorectal cancer. *Anticancer Agents Med Chem* 2013;13:11–19.
- 169 Thomas R, Holm M, Bellamy P, et al. Lifestyle factors correlate with the risk of late pelvic symptoms after prostatic radiotherapy. *Clin Oncol* 2013;25:246–51.