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

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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.11–19 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 al28 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.
**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 Exercising 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 in 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.34 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.41 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.42 43 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.44 45 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.46 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 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 51 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.34 35 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.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.37 61 It is important, therefore, that attention is given to nutritionally healthy polyphenol-rich foods that enhance upregulation of antioxidant enzymes.9 36 37 39 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.58 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 HPS 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.65 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 cancers 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.63 This is supported by a recent experiment in mice that reported a better cancer response to adriamycin with concomitant exercise.69 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

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Testosterone: High levels of androgens are associated with a higher incidence of prostate cancer, 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. It is widely stated that serum testosterone increases immediately after vigorous exercise, but this has not been confirmed in all studies. This effect also appears to be very short-lived, around 15 min to an hour after exercise. 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.

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. 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.

Irisin is a type I trans-membrane messenger protein, which is produced in muscle cells in response to exercise. One study reported that higher levels were linked to more favourable breast cancer prognostic risk at diagnosis. In laboratory studies, irisin significantly reduced cancer cell proliferation, migration and viability in malignant cancer cell lines, without affecting non-malignant cells. 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. This reduction in malignant potential of irisin, however, was not observed with colon, thyroid and oesophageal cancer cell lines. 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. However, a recent experiment used tandem mass spectometry 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.

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. 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. 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. Following moderate exercise regimes, however, particularly with regular training, most long-term studies suggest exercise improves immune function in all age groups. Its benefits are particularly clinically relevant in the elderly whose immune function is becoming less efficient, or obese individuals whose NK-cell numbers in blood and in solid organs, together with their cytotoxicity and cytokine secretion, are reduced. This also implies a benefit for individuals with impaired immunity after cancer treatments, but these studies have yet to be conducted.8

Alzheimer’s disease and atherosclerosis. 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.
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 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-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 (NFκB) 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 an 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.

Oxidative stress and antioxidant pathways

Table 1  Mainly direct biochemical changes related to exercise

<table>
<thead>
<tr>
<th>Class of effect</th>
<th>Effector molecule or gene</th>
<th>Effect of exercise on effector molecule or gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell growth regulators</td>
<td>IGF-1</td>
<td>Decreased levels52–56</td>
</tr>
<tr>
<td></td>
<td>IGF8BP3</td>
<td>Increased levels52–56</td>
</tr>
<tr>
<td></td>
<td>BRCA1</td>
<td>Increased expression50–54</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>Increased expression50–54</td>
</tr>
<tr>
<td>Proteins involved in DNA damage repair</td>
<td>RAS family oncogenes</td>
<td>Suppressed activity60</td>
</tr>
<tr>
<td>Androgen receptor coactivators</td>
<td>PSA</td>
<td>Enhanced activity51–66</td>
</tr>
<tr>
<td>Regulators of apoptosis and cell cycle arrest</td>
<td>Heat shock proteins</td>
<td>Enhanced activity51–66</td>
</tr>
<tr>
<td>Hormonal systems</td>
<td>Oestrone</td>
<td>Reduced activity88</td>
</tr>
<tr>
<td></td>
<td>Testosterone</td>
<td>Transient rise then reduced activity70–84</td>
</tr>
<tr>
<td></td>
<td>VIP</td>
<td>Transient rise then reduced activity70–84</td>
</tr>
<tr>
<td></td>
<td>Leptin</td>
<td>Reduced activity133–142</td>
</tr>
<tr>
<td></td>
<td>Irisin</td>
<td>Reduced activity133–142</td>
</tr>
<tr>
<td></td>
<td>Resistin</td>
<td>Reduced activity124</td>
</tr>
<tr>
<td>Immune system components</td>
<td>Natural killer cells</td>
<td>Enhanced activity117–124</td>
</tr>
<tr>
<td></td>
<td>White cells</td>
<td>Enhanced activity117–124</td>
</tr>
<tr>
<td>Inflammation</td>
<td>C reactive protein, interleukin-6, TNFα</td>
<td>Reduced activity93–102</td>
</tr>
<tr>
<td></td>
<td>Prostaglandins</td>
<td>Reduced activity93–102</td>
</tr>
<tr>
<td></td>
<td>COX-2</td>
<td>Reduced activity106–114</td>
</tr>
<tr>
<td></td>
<td>Glutathione, catalase and superoxide dismutase</td>
<td>Increased activity55–59 90</td>
</tr>
</tbody>
</table>

COX-2, cyclo-oxidase-2; IGF, insulin-like growth factor; IGF8BP, insulin-like growth factor-binding protein; TNF, tumour necrosis factor; VIP, vasoactive intestinal peptide.

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,146 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 weight16 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

<table>
<thead>
<tr>
<th>Associated activity</th>
<th>Effector molecule or pathway</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunlight exposure</td>
<td>Vitamin D</td>
<td>Higher146–151</td>
</tr>
<tr>
<td></td>
<td>Circadian rhythm</td>
<td>Improved152–153</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Oestrone</td>
<td>Lower29 70 117 125–143</td>
</tr>
<tr>
<td></td>
<td>Leptin</td>
<td>Lower52 116–120 122</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
<td>Greater52 116–120 122</td>
</tr>
<tr>
<td></td>
<td>Triglycerides/cholesterol</td>
<td>Reduced aggregation132–133</td>
</tr>
<tr>
<td>Mood</td>
<td>Endorphins</td>
<td>Increased release152–165</td>
</tr>
<tr>
<td></td>
<td>Monoamines</td>
<td>Higher levels162 763</td>
</tr>
</tbody>
</table>
reduction in weight. 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. In one clinical study, this was quantified as every 100 min of exercise giving a 3.6% lowering of serum oestrogen.

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. Epidemiological studies have suggested that high levels of cholesterol in the blood are associated with increased risk of cancer and progression of cancer.

Vitamin D levels and sunlight exposure: These are both higher among those who exercise outdoors regularly 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. 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. The vitamin D receptor is highly expressed in epithelial cells known to be at risk of carcinogenesis, such as the breast, skin and prostate. Higher vitamin D levels are associated with lower colorectal, breast and prostate cancer mortality. Despite this, a direct causational 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. Sunlight exposure, independent of vitamin D levels, has been linked to a lower incidence of prostate cancer. 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.

Psychological well-being: As well as being distressing, anxiety and depression have been linked to reduced survival following radical cancer treatments. 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. Another trial involving individuals from Korea with head and neck cancer reported similar findings. 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. 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. In addition, light exposure, which increases with outdoor exercise, has been linked to a reduction in non-seasonal depressive disorders.

In conclusion, clinical studies suggest a significant benefit for regular exercise after cancer for improving well-being and disease outcomes. The most feasible biochemical pathways, supporting regular exercise after cancer for improving well-being and disease outcomes, 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, 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.

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Competing interests None declared.

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

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