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Invited Review

Why exercise has a crucial role in cancer prevention, risk reduction and improved outcomes

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Abstract

Introduction: Exercise is one of several factors known to lower the risk of developing cancer, as well as improve outcomes in patients already diagnosed. People who exercise after cancer have lower rates of cancer complications, treatment toxicities, relapse and improved survival. This review highlights the supportive data and biochemical processes, which explain these potential benefits.

Sources of data: PubMed, Embase, Medline and Cochrane libraries were searched for papers which addressed the effects of exercise and physical activity on cancer for this review. The search terms used were physical activity, exercise and cancer up to February 2021. We also referred to the background research required for international exercise intervention study involving men with prostate cancer (INTERVAL-GAP4) and scrutinized references within the robust papers published on this subject to ensure we

did not miss any clinically studies. One hundred and eighty eight papers were included.

Areas of agreement: Exercise programmes mitigate many of the complications and risks associated with cancer, particularly thromboembolism, fatigue, weight gain, arthralgia, cognitive impairment and depression.

Areas of controversy: Molecular and biomarker changes, resulting from exercise, suggest that exercise elicits beneficial changes in insulin-related pathways, down-regulates inflammation and serum oestrogen levels, and enhances oxidative, immune and cellular repair pathways. Nonetheless, the evidence remains preliminary.

Growing points: The timing, intensity and challenges of prehabilitation, adjunct and rehabilitation exercise programmes are being increasingly understood but their implementation remains sporadic.

Areas for developing research: More robust clinical trial data are needed to substantiate a causal effect of exercise on overall and cancer-specific survival. These studies are ongoing. Research evaluating the most cost-efficient ways of incorporating prehabilitation, adjunct and rehabilitation programmes into routine practice would be helpful to funding bodies and health care strategists.

Key words: exercise, cancer prevention, cancer survivorship

The influence of exercise on cancer prevention

Associations between exercise and a lower risk of developing cancer have been made evident in multiple cohort studies.[1–10] These studies are open to habit-forming linkages as physically active people are less likely to smoke, are less likely to be overweight and consume more vegetables.[1,11,12] Despite these potential biases, the sheer volume of comprehensive datasets analyses conducted in different populations across the world have made legitimate efforts to adjust for other confounding lifestyle factors. This has convinced most public health bodies that exercise is one of several crucial lifestyle habits known to lower the risk of developing several different types of cancer, detailed below.[13–16]

For prostate cancer, a compelling analysis of the large Health Professional's Follow-up Study (HPFS) demonstrated that increased exercise levels were associated with a significant reduction in aggressive subtypes including incident advanced and fatal prostate cancer in a prospective cohort.[4] With respect to breast cancer, a 2016 meta-analysis based on 38 cohort studies concluded that patients who were more physically active had a lower risk of breast cancer in comparison to those who were less physically active.[17] Further studies have revealed similar reductions in risk of breast cancer among both premenopausal and postmenopausal women.[17–20] A pooled analysis of over 1 million individuals found that leisure-time physical activity was linked to a significantly reduced risk of bladder cancer.[21] A separate meta-analysis found that the risk of bladder cancer was lower for individuals with the highest level of recreational or occupational physical activity versus those who were the least physically active.[22] In a 2016 meta-analysis of 126 studies, individuals who engaged in the highest

level of physical activity had a lower risk of colon cancer with respect to those who were the least physically active.[3] Similar results have been reported for prevention of uterine, oesophageal, stomach and renal cancers.[8,23–28]

Physical activity is defined as any bodily movement by skeletal muscles that require energy expenditure, while exercise is a sub-category of physical activity which is structured and planned specifically for the purpose of maintaining or improving fitness and health. Throughout this paper, we will use these terms somewhat interchangeably although recognizing above distinctions. Although the optimal mode and dosage of exercise has not been established and specifics vary across the literature, the consensus is that individuals who exercise at a moderate intensity level (for 3–4 hours a week) or greater have approximately a 10–20% reduction in the risk of cancer compared with sedentary individuals.[13–16] Furthermore, the earlier people start exercising and the greater the number of other healthy lifestyle factors a person has, the stronger the link is to a lower cancer risk.[3,6,7,10,29,30]

The influence of exercise on cancer relapse and survival

The benefits of exercise do not stop following a diagnosis of cancer. Research findings show that regular exercise has potential beneficial effects on the survival of patients living with cancer, with the most robust evidence demonstrated in prostate, breast and bowel cancers.[1,11,31–37]

Breast cancer

In 2005, an evaluation of 2987 patients in the Nurses' Health Study found that women with breast cancer who were walking more than 3 hours a week had lower recurrence rates of breast cancer and a greater overall survival.[38] In 2008, a cohort study of breast cancer survivors identified that patients who consistently exercised for greater than 2.5 hours per week following diagnosis had a greater than 60% reduction in the risk of all deaths compared with patients who were physically inactive.[7] Similar findings were reported from other observational and cohort studies from across the world.[29,39–41] A 2019 systematic review of 25 563 patients concluded that breast cancer survivors who were the most physically active had a 42% lower risk of death from any cause and a 40% lower risk of death from breast cancer in comparison to patients that were the least physically active.[42]

Colorectal cancer

In 2002, a retrospective analysis of patients who had been recruited into an Australian cohort study revealed that those participating in recreational sport for 1–2 days per week had a 5-year overall survival of 71% as opposed to a 57% survival in non-exercisers.[5] Likewise, in the HPFS, men with colorectal cancer who exercised regularly (>27 metabolic equivalent hours/week) had a significantly lower cancer specific mortality compared with sedentary men (<3 MET hours/week).[43] Other prospective cohort studies from across the world summarized in numerous meta-analyses reported a 30–60% reduction in relapse rate, disease specific and overall death in patients with colorectal cancer who undertook regular exercise.[14,36,44–46]

Prostate cancer (CaP)

Exercise has also been shown to have a beneficial effect on tumour marker progression. In a study conducted in men with early CaP (who did not require immediate medical or surgical intervention), randomization to a formal exercise and eating well programme led to a statistically significantly lower rate of PSA progression versus standard care.[47] A further analysis of the HPFS reported that men undertaking 3 or more hours per week of vigorous activity had a 61% reduction in the risk of prostate-specific death compared with men who undertook vigorous activity for less than 1 hour per week.[1] Men who exercised vigorously 3 or more hours per week after diagnosis or men who undertook vigorous exercise both pre- and post-diagnosis had even greater reductions in all-cause mortality. This dose-effect relationship was supported by a separate prospective

Table 1 Direct biochemical changes related to exercise

Class of effect	Effector molecule	Effect of exercise on effector molecule
Cell growth regulators	IGF1	Decreased levels
	IGFBP3	Increased levels
Proteins involved in DNA damage repair	BRCA1	Increased expression
	BRCA2	Increased expression
Epigenetic expression	*RAS* family oncogenes	Suppressed activity
Regulators of apoptosis and cell cycle arrest	P53	Enhanced activity
	Heat shock proteins	Enhanced activity
Hormones	Oestrogen	Reduced activity
	Testosterone	Transient increased then reduced activity
	VIP	Transient increased then reduced activity
	Leptin	Reduced activity
	Irisin	Enhanced activity
	Resistin	Reduced activity
Immune system components	NK cells	Enhanced activity
	White cell function	Enhanced activity
	White cells	Increased circulating proportion
Inflammation	C-reactive protein, interleukin-6, TNFα	Reduced activity
	Prostaglandins	Reduced activity
	Cox-2	Reduced activity
Oxidative stress and antioxidant pathways	Glutathione, Catalase and Superoxide dismutase	Increased activity

cohort study conducted in 2011, which found that men with prostate cancer walking more than 3 hours a week was associated with an improved survival, but only if they tended to walk more than 3 miles per hour.[11]

The anti-cancer underlying mechanisms of exercise

A change in the chemical environment of blood after exercise was first highlighted in 2005 within a randomized controlled trial (RCT) involving men with prostate cancer. Serum taken from patients who undertook moderate and regular exercise (30-minutes walking per day for 6 days a week) had an almost eight times greater inhibitory effect on the growth of cultured androgen dependent prostate cancer cells compared with serum from patients in the control group.[47] Since then, researchers have demonstrated an array of direct biological, epigenetic, metabolic and inflammatory changes which occur in the body after exercise, both acutely and chronically.[44,48] The most likely direct (Table 1) and indirect (Table 2) candidates to explain the anti-cancer effects of exercise are now highlighted.

Obesity, oestrogen, leptin and weight reduction

Unwelcomed weight gain is common after breast cancer. Likewise, in a study of 440 prostate cancer

Table 2 Indirect biological benefits of exercise

Associated activity	Effector molecule or pathway	Effect
Sunlight exposure	Vitamin D	Higher
	Circadian rhythm	Improved
Weight loss	Oestrogen	Lower
	Leptin	Lower
	Triglycerides/Cholesterol	Lower
Mood	Endorphins	Increased release
	Monoamines	Higher levels

survivors, 63% were overweight or obese.[49] Regardless of the reasons for weight gain, meta-analyses have demonstrated that individuals who gain weight after cancer treatments have more frequent and severe complications and worse survival.[50] One reason for this is the neuropeptide cytokine leptin and oestrogen, which are both generated in fat cells, particularly in postmenopausal women.[51,52] Leptin is known to directly promote breast cancer by enhancing angiogenesis and cell proliferation, as well as indirectly through involvement with the oestrogen and insulin signalling pathways.[53] This explains the links between higher levels of leptin, adiposity and hormone-related cancers such as breast and ovarian.[44,54–58] Conversely, the serum concentration of other adipokines cytokines (adiponectin) is inversely correlated with adiposity and breast cancer risk, probably as a result of their anti-inflammatory properties.[59,60]

Studies have shown that targeted exercise programmes help individuals to lose weight.[35,61] It is unlikely, however, that a reduction in adiposity is a major anti-cancer mechanism because exercise programmes, at best, usually only show a modest reduction in weight.[61–64] However, even before weight reduction occurs, exercise directly lowers serum oestrogen and leptin levels and raises adiponectin levels, independent of weight loss.[63,65–67] In one clinical study, this was quantified as every 100 minutes of exercise leading to a 3.6% reduction in serum oestrogen.[68]

Testosterone

Testosterone can alter after exercise depending on the underlying level of fitness, age, exercise intensity and even mood at the time of training.[69] It is documented that testosterone increases immediately after vigorous exercise in some but not all studies.[69–73] This could be a potential concern as excess levels are associated with a higher incidence of prostate cancer.[54] In general, the increase in serum testosterone appears to be very short lived, lasting for 20–60 minutes post-exercise, with serum testosterone returning to pre-exercise levels by 2 hours.[69–71,74,75] The binding protein also rises with exercise; hence, the concentration of free and biologically active testosterone changes by very little.[76] Moreover, this transient testosterone rise has not been reported in older men, when they are at increased risk of prostate cancer.[72,73] Furthermore, over time regular moderate or intense exercise actually lowers testosterone as well as Luteinising Hormone and Follicle Stimulating Hormone due to negative feedback, which can be a symptomatic issue for younger highly trained athletes.[69–71,77–79] On the other hand, further research has identified that a healthy lifestyle, including exercise, delays the natural age-related decline in testosterone especially in those with obesity, metabolic syndrome, diabetes and dyslipidaemia.[80] Chronically, lower levels of testosterone have actually been linked to a higher risk of prostate cancer.[81]

Vitamin D levels and sunlight exposure

Vitamin D levels and sunlight exposure are both higher in patients who exercise regularly in the open air.[82] Vitamin D influence on the incidence and progression of cancer is thought to be due to its effect on cell differentiation, proliferation and apoptosis.[83–86] Although low vitamin D levels are linked to higher relapse rates after colorectal, breast and prostate cancer,[87–91] no direct causational link has been established. In addition, correcting Vitamin D levels with supplementation has not demonstrated any significant effect on the incidence and progression of cancer. Daylight exposure, independent of vitamin D levels, is linked to a lower incidence of CaP.[92] It has been postulated that sunlight exposure may have other benefits such as modulation of the immune system and the circadian rhythm.[93]

Insulin-like growth factor (IGF-1), energy metabolism and insulin resistance

After binding to its tyrosine kinase receptor, IGF-1 activates several signalling pathways, leading to the inhibition of apoptosis and the promotion of cell growth and angiogenesis.[94,95] Raised levels of IGF-1 are expected to increase tumour growth, a phenomenon which has been demonstrated in many studies together with a greater cancer risk.[96,97] An inverse relationship is reported with IGF binding protein (IGFBP3) levels, although this effect has not been confirmed in all studies.[97] Exercise has been shown to increase the levels of IGFBP3 and lower IGF-1 in a large prospective cohort study in which participants experienced a >40% reduction of cancer deaths.[44] Conversely, lower levels of IGF-1 in active patients have been linked to an improved survival.[55]

RCTs have shown that physical activity improves insulin sensitivity and glucose metabolic pathways and helps prevent weight gain especially after androgen deprivation therapy for CaP.[98–100] Hyperglycaemia and hyperinsulinemia secondary to insulin resistance are associated with an increased risk of cancer, poorer prognosis and higher risk of relapse after initial treatment.[55,95,97,101,102] Moreover, high levels of C-peptide, a marker of insulin secretion, are associated with a more than 2-fold increased risk of CaP mortality.[103] One addition factor for these worse outcomes may be a hormone called resistin, also known as adipose tissue-specific secretory factor (ADSF), which is a cysteine-rich adipose-derived hormone that increases with insulin resistance. Resistin is known to up-regulate pro-inflammatory 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 inflammation, proliferation and anti-apoptosis pathways.[104–106] Men commencing androgen deprivation therapy exhibit a rise in circulating insulin, and this hyperinsulinemia precedes changes consistent with metabolic syndrome, including adiposity, hyperlipidaemia and sarcopenia.[102,107]

DNA repair and epigenetic effects on gene expression

Exercise has been shown to influence gene expression, yet it remains unknown how these epigenetic changes have the most influence on cancer risk.[9] The GEMINAL study, is a trial involving men with low-risk prostate cancer, found a set of *RAS* family oncogenes (*RAN*, *RAB14* and *RAB8A*) to be down-regulated after a regular exercise and lifestyle initiative.[107] Within prostate tissue, RAN (Ras-related nuclear protein) has been shown to function as an androgen receptor co-activator.[107] Studies involving men on active surveillance for prostate cancer showed that >180 genes had altered expression comparing those who exercised vigorously as opposed to sedentary men.[108] Genes especially relevant exercise were those supporting DNA repair such as BRCA1 and BRCA2, those involved in signalling cell cycling and those in the histone deacetylase pathways. The up-regulation of BRCA genes after activity has been highighted in the rat mammary gland and aslo clinically in women who were BRCA 1, 2 mutation carriers.[109,110] Markers of an improved cellular repair process were also reported in a study which showed that exercise

up-regulated the key regulator gene p53 and, by doing so, encourages damaged cells to repair or if not possible, self-destruct.[109,111] Telomere length was also shown to be a prognostic marker among men with CaP on active surveillance. Men taking a moderate exercise and healthy eating programme had increased nuclear telomere length compared with sedentary men and this correlated with reduced PSA progression.[112]

Oxidative stress and antioxidant pathways

Physical activity, especially if strenuous, produces reactive oxidative species (ROS). At high concentrations, ROS are known to increase oxidative stress on DNA.[113,114] In a biofeedback reaction to this brief rise in ROS, especially after regular training, an adaptive up-regulation of antioxidant genes occurs resulting in greater formation of antioxidant enzymes such as glutathione, superoxide dismutase and catalase.[115,116] In a pilot study from California, men who reported ≥3 hours per week of vigorous exercise had modulated expression of the nuclear factor erythroid 2–related factor 2 (Nrf-2)-mediated oxidative stress response pathway in their prostate tissue compared with men who undertook less exercise.[108] Other studies have confirmed that trained individuals have greater levels of anti-oxidant enzymes which would potentially strengthen their defence against environmental and ingested oxidating carcinogens.[115,117–119] If nutritional deficiencies exist that impair the production of antioxidant enzymes, there is a danger that strenuous exercise could do more harm than good especially in the elderly, where this adaptive process is known to be attenuated.[119] It is important, therefore, that attention is given to nutritionally healthy foods that also help enhance up-regulation of anti-oxidant enzymes.[115,117–119]

Immunity function

After physical activity, higher levels of catecholamines are produced, which then encourage the recruitment of leucocytes into the peripheral blood. This up-regulates the concentration of lymphocytes and neutrophils, including natural killer (NK) cells, CD4+ T cells and B cells, potentially reducing an infection risk.[120,121] This observation was supported by a study which showed that individuals who regularly took more than 2 hours of moderate exercise per day has nearly 30% reduction in risk of upper respiratory tract infections compared with those with more sedentary habits.[122] It must be noted, however, that if exercise is too strenuous for an individual, it is followed by a transient decrease in lymphocyte concentration and impaired cellular-mediated immunity, which could potentially increase the infection risk especially after ultra-endurance running events.[123] Overall, most long-term studies suggest that the effect of moderate exercise has little influence on immune function in healthy populations, but its benefits are particularly relevant in the elderly, who commonly suffer from declining immune function.[124,125] This also implies a potential benefit for the immune function of individuals after chemotherapy; however, these studies have not yet been conducted, although preclinical research is promising.[115]

Chronic inflammation and prostaglandins

An appropriate inflammatory response is an important part of healthy immunity but persistent and low-grade chronic inflammatory activity is associated with degenerative diseases such as atherosclerosis Alzheimer's disease and cancer.[100,126] There is a general consensus that over-compensation from an ailing immune system trying to maintain immunosenescence.[123–125] In these groups, attenuated IL-2 production leads to a decreased cytotoxic capacity of NK cells and T lymphocytes on a 'per cell' basis. To compensate for this, higher levels of inflammatory cytokines stimlate Tumour Necrosis Factor, interleukin-6 and acute phase proteins, in an attempt to increase concentrations of NK cells and T-cells.[123–125,127,128] These inflammatory cytokines unfortunately promote tumour development and growth directly, or indirectly via prostaglandins; hence, the relationship between cytokines and advanced cancers is associated with an increased

risk of cancer mortality.[100,129–131] Particular attention has to be paid to the activity and downstream effects of prostaglandins. Prostaglandins are biologically active lipids generated from arachidonic acid via the enzyme cyclo-oxidase (COX). The COX-1 enzymes are present within normal tissues and are up-regulated in response to trauma, infection or chemical injury, generating an increase in prostaglandins triggering an appropriate inflammatory cascade and immune response. COX-2 is also increased by several cytokine and growth factor subfamilies, with COX-2 known to be highly expressed in many tumours.[132] Chronic inappropriate and excessive production of prostaglandins, such as prostaglandin-2 (PGE_2), have been implicated in cancer progression, apoptosis, invasion, angiogenesis and metastases.[133,134]

As well as anti-inflammatory drugs and fresh vegetables, regular non-traumatic exercise has been shown to reduce COX–2-mediated activation of prostaglandins, which could explain the reported anti-cancer properties of exercise.[135–140] For example, a study involving biopsies of rectal mucosa showed that leisure-time physical activity, particularly in overweight individuals, was associated with a 28% decline in prostaglandin E2 (PGE_2).[141]

A state of chronic inflammation is more common among individuals with poor gut health which, via reduced gut wall integrity, allows more inflammatory toxins to pass into the body.[142] Poorer gut health is more likely in overweight sedentary individuals, malnourishment, type II diabetes and the elderly.[125,127] On the other hand, recent studies suggest that exercise can enhance the number of beneficial microbial species and enrich the microflora diversity, although its cause and effect has not been established.[142–144]

Muscle as an endocrine organ

It is now well established that the muscular system is the largest endocrine organ in the body producing a range of hormones and cytokines signalling all other tissues, organs and systems.[145] During activation of muscle, as occurs in exercise, a range of molecules are released many of which have been demonstrated to have cancer suppressive effects directly and by facilitating the release of immune cells, their activity and surveillance ability.[146] This may in part explain why patients with cancer that have low muscle mass experience greater disease and treatment issues and have compromised survival. Resistance training and other exercises are best strategy available to maintain or increase muscle mass and are recommended in most national statements on exercise for cancer care.[147] The larger the muscle mass of the patient, the greater production of anti-cancer molecules, and this muscle mass should be activated frequently, preferably daily at an intensity sufficient to dose the cancer with this ‘exercise medicine’.

Exercise, quality of life and toxicity

Adverse cancer-related symptoms, which have been shown to be alleviated by exercise, include fatigue, muscle weakness, thromboembolism, weight gain, loss of bone density, quality of life (QOL), psychological distress, incontinence and sexual dysfunction.[49]

Physical activity improves well-being after cancer

Through a combination of earlier detection and enhanced multidisciplinary management, the chances of surviving cancer are significantly improving year by year. Unfortunately, many of these individuals suffer from both acute and long-term physical and psychological adverse effects. These ongoing adverse toxicities affect their personal QOL as well as impacting substantially on their families, and their ability to regain fiscal autonomy. The adverse effects of cancer often result in the need for more frequent and costly medical interventions to manage chronic conditions including arthritis, depression, heart disease and diabetes. Fortunately, a physically active lifestyle and, particularly, supervised exercise rehabilitation programmes after cancer are linked to an improvement in many common adverse effects across multiple types of cancer. This has been

exhibited in patients receiving surgery, radiotherapy, chemotherapy, hormonal and biological therapies for cancer.[148,150–153]

Cancer-related fatigue

Cancer-related fatigue (CRF) is one of the most disturbing symptoms experienced by men and women during and after anti-cancer management. It is reported in up to 90% of patients during chemotherapy, radiotherapy or after surgery, and nearly 40% of patients taking hormone or biological therapies.[154] Exercise interventions modestly improve CRF as revealed in a review 28 RCTs involving participants undertaking a range of exercise programmes.[155] This was confirmed in a further meta-analysis of 18 RCTs which also sub-divided the participants into home-based exercise programmes and supervised exercise programmes, which included a combination of aerobic and resistance exercises.[166] In this study, a statistically significant benefit of exercise for CRF was observed in breast cancer patients involved in supervised exercise programmes but not home-based programmes.

Anxiety, low mood and depression

Anxiety, low mood and depression are reported in 25–30% of patients after cancer.[156] Exercise, especially if combined with relaxation, helps to elevate mood and self-esteem, enhance compliance to medical interventions, reduce depression and anxiety and reduce fears of relapse.[67,156–168] In addition, light exposure, which increases with outdoor exercise, has been linked to a reduction in non-seasonal depressive disorders.[163] As well as being emotionally distressing, individuals suffering from the psychological consequences of cancer have a lower survival in comparison to those free of psychological distress.[162–167] Of note, a large prospective cohort study from California reported that 4.6% of 41 000 men who were clinically depressed after prostate cancer had a 25% reduction in disease-specific survival compared with non-depressed men.[167] Another trial involving individuals from Korea with head and neck cancer reported similar findings.[168] The mechanism by which exercise helps fight depression has not yet been firmly established but hypotheses include increased endorphin and monoamine release, mental distraction and rises in core body temperature.[163]

Physical fitness and QOL

In a study involving patients with colorectal cancer, patients undertaking at least 150 minutes of physical activity per week had an 18% higher QOL score than those who reported no physical activity.[168] Another study showed similar benefits for breast cancer survivors who had completed surgery, radiotherapy or chemotherapy, and also demonstrated that change in peak oxygen consumption correlated with change in overall QOL.[160] A meta-analysis of 34 randomized trials published in the BMJ involving patients who undertook exercise after cancer showed improvements in muscle power, hand grip and exercise capacity as well as an enhanced mood and greater QOL, with reduced fatigue, anxiety and depression.[149] Other large meta-analyses from the USA and Australia have confirmed similar benefits.[32,169]

Arthritis

Arthritis affects 55% of cancer survivors, impacting mobility and increasing the requirement for anti-inflammatory medication, which can result in cardiac and renal damage.[178] Several factors conspire to accelerate the natural tendency for humans to develop joint pains. These include surgery, chemotherapy and biological therapies, in particular hormonal treatments such as aromatase inhibitors (AI's). Not only is the swelling, pain and stiffness associated with arthritis troublesome, it can also affect compliance, potentially compromising the effectiveness of adjuvant therapies.[170,171] Furthermore, the symptoms of arthralgia can indirectly exacerbate other complications of cancer by restricting an individual's ability to mobilize freely. These complications include osteoporosis, hot flushes, weight gain and indeed a greater risk of cancer

relapse. In the general population, people who exercise have a lower incidence of arthritis. In addition, the landmark HOPE study from New York reported significantly enhanced joint function in breast cancer patients randomized to a supervised exercise and stretching programme when taking AI's.[173]

Bone mineral density loss

Bone mineral density (BMD) loss is a prominent concern among both male and female cancer survivors. Premenopausal women following breast cancer are at increased risk because of reduced levels of oestrogen triggered by premature menopause due to chemotherapy, surgery or hormonal therapy. Men taking hormone deprivation therapy for CaP are also at an increased risk for developing osteoporosis.[172,173] Lifestyle factors linked to an increased risk of developing osteoporosis include a low calcium and vitamin D intake, a diet low in plant-based protein, lack of physical activity, smoking and excessive alcohol intake.[175] A number of studies have linked regular physical activity with an ameliorated risk of bone mineral loss.[172,173] An RCT involving women with breast cancer were randomized to standard care or an exercise intervention of either resistance exercise (with bands) or aerobic exercise (jogging or fast walking).[172] In this study, the rate of decline in BMD was significantly less in the resistance exercise group, with a greater benefit seen in the aerobic exercise group particularly among premenopausal women.[172] Declining bone density is particularly problematic in men on androgen deprivation therapy for their prostate cancer with one RCT demonstrating resistance training to be ineffective; however, the combination of resistance training and impact exercise (skipping, hopping, bounding) completely nullified the bone loss.[172]

Thromboembolism

Thromboembolism remains a significant risk for patients with malignancy, particularly those with pelvic involvement, those who underwent recent surgery and/or chemotherapy or those who have a history of immobility, varicose veins or thromboses.[174] Although strategies such as compression stockings, warfarin and low molecular weight heparin are essential, early mobilization and exercise remains an important practical aid in reducing this life-threatening complication.[50,153]

Other conditions improved with exercise

Constipation caused by immobility, opiate analgesics or anti-emetics during chemotherapy is a significant patient concern. Exercise reduces bowel transit time and ameliorates constipation and its associated abdominal cramps.[155] Exercise has been linked to lower cognitive impairment from chemotherapy (Chemo-brain) and hormonal therapies.[49,147–150]

Discussion and conclusions

The importance of physical activity before, during and after cancer treatments is being appreciated as emerging evidence indicates that exercise improves several common side effects associated with cancer therapies and correlates with an improved overall survival and a lower probability of relapse. The most feasible biochemical pathways, supporting a direct and indirect anticancer mechanism of action, have been summarized in this article, but there are likely to be others which remain undiscovered. Furthermore, it remains unclear which of these mechanisms plays the most important role, whether they are person or disease-dependent and whether they could be enhanced by diet and other lifestyle modifications.

It also appears that it is never too late to start exercising with cancer. The clinical value of physical fitness prior to surgery is well established. Physically fit surgical candidates have lower peri-operative complication rates and quicker recoveries compared with their less-fit counterparts.[180–183] It is likely that prehabilitation may also help mitigate an increase in COVID-19 surgical morbidity and mortality.[177] Beyond surgery, better physical function, muscle volume and exercise levels have been connected to higher rates of response and enhanced tolerance

to chemotherapy, hormone therapies, radiotherapy and even the newer targeted immunotherapies.[7,176–180] There is growing interest in exercise during chemotherapy administration as a way to alter blood flow and tumour microenvironment making cancer cells more susceptible to treatments, although more clinical research is required before exercise bikes are routinely implemented into chemotherapy units.

Dozens of interventional studies have tested the feasibility and potential benefits of exercise in cancer survivors.[33,34,37] Despite the benefits, implementation of formal prehabilitation and rehabilitation programmes for patients with cancer across the UK tends to be sporadic and exercise levels after cancer remain low.[180] The exception is private hospital groups such as Genesis Care, which have routine exercise medicine facilities in most of their chemotherapy and radiotherapy centres.[182] Wider funding for a national exercise programme has been hampered by the shortage of RCT's and cost effectiveness research. Macmillan Cancer Care is collaborating with the Royal College of Anaesthetist and National Institute of Health research (NIHR) to develop these principles and guidance together with an action plan.[182] This sets out how NHS organizations across the UK can replicate some of the pioneering work already taking place at a limited number of Trusts. In particular, it is developing formal guidance for patient identification and prioritization for a prehabilitation and collaborative, inter-professional program exercise prescription considerations and parameters, and effectiveness monitoring and follow-up. In the meantime, the results of several large randomized clinical trials are eagerly awaited, which are evaluating the potential magnitude of the effect which physical activity and/or exercise interventions have on cancer patients and survivors (188). These include the BreastCancerWeightLoss(BWEL)trial in newly diagnosed breast cancer patients, the CHALLENGE trial in colon cancer patients who have recently completed chemotherapy and the INTERVAL-GAP4 trial in men with metastatic, hormone-sensitive or castrate-resistantprostatecancer.[159,183]

Data availability statement

No new data were generated or analysed in support of this review.

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