# Unleashing anti-tumour immunity: dietary restriction and exercise interventions adjunct to chemotherapy for cancer patients

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## ABSTRACT

*Conventional chemotherapies can stimulate the immune system by increasing tumour antigenicity (e.g., neoantigen exposure to immune cells) and altering adjuvanticity in the tumour (e.g., danger associated molecular patterns and cytokines). These molecules promote the recruitment, activation, and maturation of dendritic cells, which in turn, prime and activate cytotoxic T cells against tumour cells. However, several factors can decrease the immunostimulatory efficacy of chemotherapeutic agents. These include reduced tumour cell antigenicity and adjuvanticity and compromised immune function at a local and systemic level. Findings from preclinical studies show that dietary restriction and exercise promote systemic changes that may help to restore immune system function through several mechanisms, including an enhanced infiltration and function of antitumoral immune cells and a decrease in immunosuppressive cells, leading to a reduction in tumour volume. In addition, dietary restriction and exercise training in mice have been shown to enhance the efficacy of chemotherapy. In human studies there is also emerging evidence that dietary restriction and exercise can impact the immune system towards a more antitumoral profile. In this review, we discuss the immunostimulatory effects of dietary restriction (caloric restriction and fasting) and exercise training in preclinical cancer models, and potential synergies with chemotherapy. We then review clinical studies assessing the effects of these interventions on immune-related endpoints and tumour responses. Finally, we propose that combining dietary restriction with exercise could be a promising strategy to increase chemotherapy efficacy.*

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## INTRODUCTION

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 alone (189). Treatment often includes combinations of surgery, radiotherapy, and/or systemic therapy (chemotherapy, hormonal treatments, targeted biological therapies, immunotherapy) (189). Chemotherapy is a systemic cancer treatment that often targets cancer cells during division, leading to cell death and tumour shrinkage (190). It can be given as a definitive primary treatment to destroy all tumour cells, or as neoadjuvant or adjuvant therapy administered prior to or after locoregional treatments to increase their effectiveness. If cure is not possible, chemotherapy may be used as a palliative treatment to relieve disease symptoms or to temporarily arrest disease progression (190).

It is widely established that anti-tumour immune responses contribute to the success of chemotherapy agents (61, 185). Supporting this concept, there is a link between tumour lymphocytic infiltrates and improved patient prognosis (58, 144) and with higher responses to neoadjuvant chemotherapy in breast cancer (42, 85). In mouse models, the efficacy of conventional chemotherapies is much higher in immunocompetent animals than their immunodeficient counterparts (61, 95, 105, 185). This provides the rationale for the combination of chemotherapy and immune checkpoint inhibitor-based immunotherapy in cancer treatment, as certain chemotherapeutics are hypothesized to convert "cold" tumours into "hot" tumours and thereby sensitize cancers to immune checkpoint inhibitors. Consequently, this combination is currently used in patients with certain types of cancer (61, 95). Nevertheless, in some cases, combining chemotherapy and immunotherapy may increase treatment side effects such as acute kidney injury (65). An alternative approach to enhance the efficacy of chemotherapeutics could be the addition of dietary manipulation (e.g. caloric restriction, fasting or fasting mimicking diets) and exercise programs, as these interventions have been demonstrated to independently improve several aspects of immune function and to suppress tumour growth in preclinical studies (40, 93, 94, 120), as well as improve patient-related outcomes in clinical studies, with few or no side effects (30, 102, 175). Our focus in this review is to present the scientific premise by which dietary restriction and exercise have the potential to restore and potentiate antitumoral

immunological responses in the setting of chemotherapy. To this end, we will first highlight the importance of the host immune system to support chemotherapy efficacy. We will then review preclinical and human studies reporting how dietary restriction and exercise interventions exert immune mediated antitumoral effects, modulate the microbiome and synergize with chemotherapy. Finally, we will review studies combining dietary restriction with exercise, and summarise how these combinations may augment antitumoral-immunity and thus culminate in enhanced clinical responses to chemotherapy.

## IMPORTANCE OF THE IMMUNE SYSTEM FOR CHEMOTHERAPY SUCCESS

Chemotherapeutic agents can promote the activation of an antitumoral immune response by inducing crosstalk between tumour cells and elements of the immune system through cellular stress-related processes termed immunogenic cell death (ICD) and immunogenic modulation (53, 61, 95). Chemotherapy-driven ICD is mediated by two processes that determine the immunogenicity of the tumour cells: antigenicity and adjuvanticity (53, 61). Antigenicity is the presentation of antigens via MHC-I on tumour cells; these antigens can be expressed only by tumour cells, and are termed tumour-specific antigens or neoantigens, or they can be overexpressed in tumour cells but also expressed on healthy cells and are termed tumour-associated antigens (53, 166). Chemotherapy-induced cell stress promotes the expression and presentation of tumour-specific and tumour-associated antigens and MHC-I on tumour cells (61, 80, 95, 106). Adjuvanticity refers to the cell surface exposure and release of immunostimulatory molecules from dying tumour cells named danger associated molecular patterns (DAMPs), of which the best studied are calreticulin, ATP, high mobility group box 1 and type-I IFNs (53, 61, 95). Cognate receptor binding of DAMPs on antigen-presenting cells such as dendritic cells, promotes their recruitment and phagocytosis of antigens released by dead tumour cells, which leads to their activation and maturation (53, 61, 95). Dendritic cells can cross-present the exogenous engulfed tumour antigens onto MHC-I molecules to prime naive CD8 T cells in the lymph nodes and provide co-stimulatory molecules and cytokines for full T cell activation, hence stimulating an adaptive anticancer response (61, 95) . Moreover, dendritic cells also present antigens on MHC-II molecules to CD4+T cells and induce their activation and differentiation into different subsets (104). Although they are usually less considered in the context of antitumoral immunity, CD4+ T cells have important antitumoral roles, including the provision of help to CD8+ T cells, the support for antigen-presenting cells, and the activation of B cells for the secretion of antibodies against tumour antigens (8, 158). Importantly, tumour cells are also able to express MHC-II molecules, and CD4+ T cells can have direct cytotoxic activity against tumour cells under certain conditions by recognizing the antigens presented in these MHC-II molecules (8, 158).

Chemotherapy can also render cancer cells more susceptible to immune-mediated killing without inducing classic ICD through a process called immunogenic modulation (53). Immunogenic modulation can occur when chemotherapy-induced cell damage does not result in cell death but there are alterations in the biology of tumour cells that make them more susceptible to killing by innate and adaptive immune effectors (53). These alterations include changes in surface marker expression that sensitizes tumour cells to CD8+ T cells and NK cells killing, and downregulation of anti-apoptotic and/or pro-survival genes (53, 67).

Chemotherapy efficacy can be lost or reduced in several ways (61). First, antigenicity of tumour cells may be reduced by losing tumour antigens through selection pressures that facilitate the expansion of cell clones that do not express antigens recognized by the immune system (61, 63), or by downregulation of MHC-I (61, 166, 186). Second, tumours can lose adjuvanticity due to alterations in the secretion or exposure of DAMPs or activation of mechanisms that antagonize DAMPs (61, 186). Finally, the efficacy of chemotherapy can be reduced by any microenvironmental or systemic immune defect (61, 185). Microenvironmental immune defects include low infiltration of immune effectors into the tumour microenvironment (TME) (the heterogenous milieu of molecules, blood vessels, and tumour, immune and stromal cells), exhaustion or anergy of CD8+ T cells or suppression of their activity by tumour cells, the infiltration of immunosuppressive cells (cells that inhibit the antitumoral response, promoting tumour immune escape) into the TME such as regulatory T cells (Tregs), M2-subtype macrophages, N2-subtype neutrophils, and myeloid-derived suppressor cells (MDSCs), or by immunosuppressive environmental conditions such as hypoxia and low pH (61, 100, 166, 185). At the systemic level, immunosuppressive alterations of the gut microbiota may also compromise the efficacy of chemotherapy (61, 71). There is growing evidence regarding the interplay between the gut microbiota and host immune system (84, 182), which can impact cancer immune surveillance (182, 184). Of note, the use of antibiotics in mice or using germ-free mice has been shown to reduce immune responses and the efficacy of different ICD inducers and immunotherapy (84). Therefore, improving the immunological competence of the patient and the tumour microenvironment is of paramount importance to increase chemotherapeutic efficacy.

## EFFECTS OF DIETARY RESTRICTIONS

Dietary restrictions include caloric restriction and fasting regimens. Caloric restriction is defined as a reduction in total daily energy intake by 15-30%, without changing the macronutrient ratio (159). Fasting includes various eating regimens: water-only fasting or a restriction of over 50% of the usual calorie intake, lasting between 24 hours and several days; time-restricted feeding where eating is limited to a 6-to-12-hour window; and fasting-mimicking diets (FMD) where eating is limited to low calorie, low protein, low sugar, plant-based foods (19, 165). When caloric intake is reduced through dietary restriction starvation is induced which leads to systemic changes in the levels of circulating hormones and metabolites,

including low levels of glucose, insulin, insulin-like growth factor 1 (IGF-1) and leptin, high levels of glucagon, ketone bodies and adiponectin. These changes result in an increase in glycogenolysis, lipolysis, hepatic gluconeogenesis, and protein catabolism and a decrease in muscle uptake of glucose (41, 120). At the cellular level, these changes modulate key molecular cascades to counteract the metabolic stress (41, 120). In the context of cancer, caloric restriction and fasting regimens have been shown to have beneficial effects on tumor incidence, progression, metastasis, and survival in various animal models with normal weight (13, 44, 60, 101, 120, 178). Moreover, population-based studies in humans indicate that caloric restriction may reduce cancer incidence and cancer mortality rates (26, 81). Such anticancer effects are thought to be mediated through a reduction of circulating glucose, insulin, and IGF-1, which affects the ability of malignant cells to survive or adapt and induce an alteration of the systemic immune state to promote an antitumoral immune response (40, 41, 120, 124, 159).

**Immune mediated antitumoral effects of dietary restriction**

Caloric restriction and fasting regimens have been shown to influence the immune system (41, 120, 132) and synergize with immunotherapy in preclinical models (2), confirming these immunomodulatory effects. Caloric restriction and fasting regimens may boost anti-tumour immune responses by improving antitumour immunity effectors and decreasing local immunosuppression (40). Moreover, these interventions have beneficial effects on the gut microbiome, which may in turn promote a more appropriately responsive immune system (132).

*I. Improved antitumoral immunity.*

Evidence for a beneficial effect of caloric restriction or fasting regimens on the regeneration of progenitor immune cells and maintenance of memory T cell subsets with an enhanced antitumoral function has been obtained from preclinical studies. The reduction of IGF-1 and protein kinase A activity induced by several cycles of short-term fasting in mice led to signal transduction changes in long-term hematopoietic stem cells, increasing hematopoietic stem cell protection, self-renewal, and regeneration (28). Importantly, several cycles of short-term fasting also diminished immunosuppression and mortality caused by chemotherapy (28). Similarly, an FMD increased the number of CD8+ circulating lymphocytes by a third and the number of common lymphoid progenitor cells by two-fold in the bone marrow (44). Short-term fasting (155) and caloric restriction (34) have also been reported to increase the number of naïve CD4+ and CD8+ T cells (155) and memory CD4+ and CD8+ T cells (34) in the bone marrow of mice, due to an increased migration from secondary lymphoid organs and blood, which is thought to aid survival and maintain T cell functionality under unfavourable conditions such as during nutritional restriction (34, 155). Importantly, the caloric restriction-induced memory T cell homing to the bone marrow was associated with an increased antitumoral effect against melanoma tumours in vivo (34) (Table 1). The level of glycolytic activity in T cells also influences the maintenance of memory CD8+ T cells, the differentiation of effector CD8 T cells is impacted (153). Indeed, effector T cells rely on glycolysis rather than oxidative phosphorylation to facilitate faster proliferation (110). Consequently, effector T cells may have difficulty competing with tumour cells for glucose under fasting conditions (40). However, glycolysis may reduce longevity of T cells (91, 153). Inducing a high glycolytic activity in CD8+ T cells compromises the generation of long-lived memory cells and, conversely, limiting glycolysis with the glucose analogue 2-deoxyglucose in CD8+ T cells ex vivo triggers the activation of starvation signalling, favouring memory versus effector differentiation (153). Notably, when CD8+ T cells primed in the presence of 2-deoxyglucose were adoptively transferred into mice bearing melanoma tumours, they had higher antitumor capacity compared to T cells cultured without 2-deoxyglucose, prolonging survival in mice (153). Therefore, limiting glucose availability through caloric restriction or fasting regimens may promote similar effects. In a recent preclinical study, short-term fasting of 48 hours in mice bearing lung tumors improved the efficacy of anti-PD1 and anti-PD-L1 treatments, increasing survival (2). Importantly, 50% of the mice treated with anti PD-1 therapy and short-term fasting had a complete response, and were resistant to a tumor rechallenge, implying that they had developed immune memory against this type of tumor (2). Furthermore, the combination treatment increased the tumor infiltration of NK and CD8+ T cells and decreased the number of Tregs, whereas depletion of CD8+ T cells abrogated the antitumor efficacy of short-term fasting and anti PD-1 treatment (2). The efficacy of the treatment was also dependent on the reduction of IGF-1 levels and autophagy in tumor cells induced by short-term fasting (2) (Table 1). Taken together, this demonstrates that fasting induced reduction of IGF-1 levels may help to restore the antitumoral immunity through a mechanism that involves increased autophagy in tumor cells, synergizing with anti PD-1/PD-L1 immunotherapy.

*II. Decreased local immunosuppression.*

It has been reported from preclinical studies that caloric restriction and fasting regimens reduce the number of immunosuppressive cells in the tumour microenvironment. Both a daily 20% caloric reduction compared to ad libitum mice and an FMD significantly reduced the infiltration of MDSCs within tumours and retarded tumour growth (133) (Table 1). Similarly, two short-term fasting periods of 48 hours in mice decreased the infiltration of MDSCs in the spleen, suppressing tumour growth as efficiently as chemotherapy (60) (Table 1). Alternate day water-only fasting has also been shown to reduce the number of M2-subtype macrophages through the induction of autophagy in tumour cells (154). Autophagy is a lysosome-mediated process by which cells eliminate damaged or unnecessary proteins and organelles and excised genomic fragments (81, 124) and is highly induced under fasting conditions (81, 130). Culturing colon tumour cells in fasting conditions increases autophagy and reduces the expression of CD73, an ecto-enzyme that converts extracellular AMP into immunosuppressive adenosine, hence reducing adenosine levels and decreasing the polarization of macrophages into the immunosuppressive subtype M2 (154). In vivo, short-term fasting leads to reduced levels of M2 macrophages and reduced tumour growth, demonstrating that fasting has antitumoral effects through autophagy-induced reduction in M2 macrophages (154) (Table 1). Autophagy-defective tumour cells upregulate ecto-ATPase CD39 that converts extracellular ATP into AMP and ADP, promoting the formation of adenosine and attracting immunosuppressive Tregs expressing adenosine receptors into the tumour bed (130, 131). Hydroxycitrate, a caloric restriction mimetic that induces autophagy and mimics the metabolic effects of fasting, caused Treg depletion in a Kras-

induced lung cancer model in mice and reduced tumour growth (131). However, in transgenic mice overexpressing CD39 in the tumours, this failed to reduce tumour growth, underscoring the importance of inducing autophagy in tumour cells for Treg depletion, which in turn improves immunosurveillance (Table 1).

Fasting-induced changes in tumour cell metabolism may also decrease the excess lactate they produce, and the consequent low pH, which are strong immunosuppressants (110) . Tumour cells are characterized by high glucose uptake and a high glycolytic rate rather than using oxidative phosphorylation, regardless of oxygen concentration, resulting in high lactate production, a phenomenon known as the "Warburg effect" (38, 40). Colon carcinoma cells cultured in conditions mimicking starvation (low glucose and low serum) for 48 h, showed a metabolic shift, down-regulating glycolysis while up-regulating oxidative phosphorylation, promoting an "anti-Warburg effect" and decreasing extracellular lactate concentration (15). In vivo, short-term fasting had a transient effect on tumour growth, slowing it during the fasting but not during the post-fasting period (15). Notably, short-term fasting had an additive effect when combined with oxaliplatin, demonstrating a higher reduction in tumour growth than oxaliplatin alone (15).

*III. Modulation of the microbiota*

Both caloric restriction and fasting regimens have been shown to modify the types and abundance of gut bacteria in preclinical models and in humans (92, 132, 135). In rodents, caloric restriction can increase the abundance of probiotic bacteria (e.g., Bifidobacterium and Lactobacillus spp.) (132). In human studies, time-restricted feeding, and short-term fasting regimens, such as Ramadan and Buchinger fasting, promote the enrichment of Faecalibacterium, which produces short-chain fatty acids (SCFAs) from dietary fibre (57) . SCFAs modulate the interaction between the gut microbiota and the immune system and induce a wide range of beneficial effects (132). Notably, the SCFA butyrate has been associated with cancer prevention and enhanced treatment efficacy (132). Moreover, caloric restriction reduces the ratio of Firmicutes/Bacteroidetes (184). These are two primary phyla in the gut, and a high ratio has been associated with various conditions, such as obesity and cardiovascular disease (157), and to a decreased response to different anti-cancer therapies (chemotherapy or a combination of chemo- and immunotherapy) (78). Ramadan and Buchinger fasting regimens have also been demonstrated to increase the abundance of *Akkermansia muciniphila* in humans (57, 151, 152), which has been linked to cardiometabolic health in mice (22). Interestingly, intravenous injection of *Akkermansia muciniphil*a-derived extracellular vesicles in immune-competent mice reduced the tumour growth of prostate cancer and increased the proportion of CD8+ T cells with an activated profile and the recruitment and polarization of macrophages into a M1 profile (107). In the context of cancer therapy, its presence is associated with a better response to anti PD-1 immunotherapy and increased infiltration of immune cells in the TME (78, 180). Therefore, it may well be that the antitumoral immune system may be enhanced by altering the gut microbiota through fasting. Nevertheless, correlation does not imply causality, and prospective studies should validate if these potentially beneficial shifts in the gut microbiome induced by dietary restriction cause an increased response to chemotherapy or immunotherapy.

**Synergy between dietary restriction and chemotherapy**

The therapeutic synergy of caloric restriction or fasting regimens with chemotherapy has higher antitumoral efficacy than either intervention alone, extending survival in different murine cancer models (18, 41, 101, 120). When combining caloric restriction or fasting regimens with chemotherapy, a differential stress response between cancer and normal cells is observed, whereby normal cells become protected against toxins (differential stress resistance, DSR) and cancer cells are sensitized to toxins (differential stress sensitization, DSS), leading to a major delay in cancer progression (38, 101).

Importantly, the synergy between fasting regimens and chemotherapy seems to depend on the antitumor immune system, as the ability of fasting to synergize with chemotherapy is abolished in athymic mice or mice depleted of CD8+ T cells, or when non-immunogenic chemotherapeutics such as cisplatin are used (44, 130, 131). Thus, Di Biase et al. showed that in a breast cancer model, FMD cycles combined with ICD inducers (doxorubicin and cyclophosphamide) increased circulating CD8+ T cells and delayed tumour progression, an effect lost upon CD8+ T cell depletion (44). Microarray analysis showed that in tumor cells, compared to normal cells, FMD induced the downregulation of Heme oxygenase (HO-1) expression, which protects against oxidative damage and apoptosis (44). The researchers demonstrated that reduced tumour cell HO-1 mediates, at least in part, the anticancer effect of FMD by increasing CD8+ T cells in tumours and their expression of granzyme-B, and by decreasing Treg infiltration (44) (Table 1).

Autophagy in tumor cells is also involved in the immune-mediated synergy between caloric restriction or fasting regimens and ICD inducers (130). A proficient autophagy response in tumour cells is needed for cross- presentation of tumor derived antigens by dendritic cells that prime CD8+ T cells against tumor cells (62). This effect may be mediated through increased adjuvanticity of dying tumor cells due to the autophagy-induced delivery of some DAMPs such as ATP and HMGB1, which attract dendritic cells into the tumour bed (62, 95). Indeed, autophagy is a causative factor for ATP secretion during chemotherapy-induced ICD (95), and autophagy-deficient cancer cells fail to induce an anti-tumour immune response in immunocompetent hosts due to an impaired capacity to release ATP in response to chemotherapy (62, 131). Furthermore, autophagy can enhance tumor cell antigenicity, as autophagy-dependent degradation of tumour antigens increases MHC-I presentation in dying tumor cells, which leads to greater CD8+ T cell responsivity and decreased tumor growth in vivo (27). Interestingly, markers of autophagy are correlated with increased CD8+ T cell/Treg cell ratios and good prognosis in cohorts of triple negative breast cancer (95). The increased stimulation of autophagy by fasting regimens may boost the therapeutic efficacy of ICD inducers by an improved antitumor immunity (24, 62). Castoldi et al. (24) reported that short-term fasting improved the capacity of mice to mount an antitumor immune response against fibrosarcoma cancer cells injected 7 days after being vaccinated with the same cell line treated in vitro with mitoxantrone (MTX) to induce ICD. Notably, when fasted mice were treated with dimethyl α-ketoglutarate, an inhibitor of starvation-induced autophagy, the percentage of tumour-free mice decreased by 55%, indicating that starvation has immunostimulatory effects

when combined with ICD-inducing chemotherapy through an enhanced autophagy in tumour cells (24). They further showed that the efficacy of MTX was independent of the autophagy competence of the host (24). In another fibrosarcoma preclinical study, hydroxycitrate (a caloric restriction mimetic that induces autophagy and mimics the metabolic effects of fasting) or short-term fasting combined with ICD-inducing chemotherapies enhanced tumour growth control as compared to either treatment alone, an effect depending on CD8+ T cells (131). They also demonstrated that low levels of IGF-1 induced by hydroxycitrate (or short-term fasting) combined with ICD-inducers can trigger an autophagy-dependent anticancer immune response that relies on extracellular ATP and low levels of Tregs in the tumour (131).

Nevertheless, the role of autophagy in the context of cancer is controversial. It is tumour suppressive since defects in autophagy can drive DNA damage, genomic instability, mitochondrial defects, and tumour growth in preclinical models. Conversely, it can be pro-tumoral, as established tumours can utilize autophagy to cope with stressors such as hypoxia, damaging stimuli, and nutrient deprivation (5, 62, 124). Therefore, additional work is required to understand how and when to inhibit or activate autophagy to develop therapeutic strategies to increase the effects of chemotherapy and improve clinical outcomes in cancer patients.

**Fasting regimens in clinical trials in cancer patients**

Clinical studies of short-term fasting or FMD in patients undergoing chemotherapy support their feasibility and overall safety, with no serious fasting-side effects and no significant reductions in body weight observed (9, 12, 39, 55, 77, 138, 164, 167, 187). Moreover, short-term fasting and FMD reduced side effects such as nausea, vomiting, fatigue and DNA damage in peripheral blood mononuclear cells and improved quality of life in patients undergoing chemotherapy (12, 48, 138, 164, 187). Furthermore, there is some evidence that FMD can improve antitumoral immune responses (Table 2). Thus, in a single-arm trial in patients with different neoplasms, an FMD in combination with standard antitumor therapies downregulated circulating immunosuppressive myeloid cell subsets and increased cytolytic NK cells and CD8+ T lymphocytes with an activated/memory phenotype (167). In a subset of breast cancer patients from the ongoing DigesT trial (NCT03454282) adhering to an FMD before surgery, the surgical tumour sample showed a significant decline in IGF-1R expression and increased CD8+ T cell infiltration compared to the paired pre-FMD biopsy analyses. Additionally, RNA-seq analyses revealed upregulation of immune signatures previously associated with good prognosis and/or better response to therapies in patients with cancer, and an increase in NKT cells (a subpopulation of T cells that express a limited repertoire of T cell receptors (TCRs) and a number of cell surface molecules in common with NK cells), activated dendritic cells and memory CD4+ and CD8+ T cells (167). In peripheral blood, FMD increased dendritic cells, NK cells, B cells and several subsets of memory T cells, and reduced exhausted T cells, Tregs, and MDSCs(167). Notably, short-term fasting and FMD have also been shown to reduce chemotherapy induced damage in T cells (37, 39, 48) (Table 2). Although very limited, the available clinical evidence related to cancer-related outcomes is promising. In a feasibility trial of an FMD in patients with breast cancer undergoing active treatment, patients receiving endocrine therapy showed longer progression free survival than the average in those settings (164). In a similar fashion, De Groot et al. showed in a phase II randomized trial that a radiologically complete response and a 90–100% tumour-cell loss in intention-to-treat and per protocol analyses, respectively, was more likely to occur in patients adhering to a 4-day FMD during neoadjuvant chemotherapy cycles compared to patients consuming their regular diet (37) (Table 2). Of note, only a third of patients in this study were able to complete at least 4 FMD cycles. The study used a standardised kit of foods consisting of soups, broths, teas and snacks, and the main reason for the low compliance was the dislike of some of the food items provided. Additional challenges to compliance in the clinical setting may include the impact of these interventions in the patients' daily routines and social interactions. To optimize compliance, future clinical studies in the cancer population could incorporate a higher variety of options, explore other less restrictive interventions such as time-restricted eating, and having support from dieticians to tailor the diet plan to address clinical needs (e.g., patients with low body mass index).

## EFFECTS OF EXERCISE TRAINING

It has been extensively reported from preclinical studies that exercise training can reduce tumour incidence, tumour growth, and metastasis in different transplantable, genetic, and chemical-induced tumour models (30, 83, 178). Observational findings in patients with cancer include an inverse association of physical activity levels and all-cause and cancer-specific mortality in those with a diagnosis of breast, colorectal, or prostate cancer, with relative risk reductions up to 40% and 60% for disease progression and risk of disease-related death, respectively (86, 113, 143). It is hypothesized that exercise controls tumour progression through effects on tumor intrinsic factors (cell growth rate, metastasis) and via modulation of systemic factors that can influence several cancer hallmarks in the TME (tumor cell metabolism, angiogenic signaling pathways, hypoxia, immune modulation) (6, 83, 89).

**Immune-mediated antitumoral effects of exercise**

Physical exercise augments the anti-tumour immune response, modulating the tumour microenvironment by acting on the innate and adaptive immune systems (30, 83, 89, 93). Notably, epidemiology studies show that the benefit of physical activity occurs in cancers with higher numbers of mutations, which determine the immunogenicity of tumour cells, as somatic mutations generate neoantigens that will be recognized by CD8+T cells (51). Conversely, physical activity shows less benefit in cancers with lower numbers of mutations (51). This implies that the immune system is also a substantial contributor to the anti-cancer effects of physical activity in humans (51). Exercise-induced reductions in tumour growth have been shown to be dependent on CD8+ T and NK cells in several preclinical studies (51, 70, 74, 128, 137, 171) (Table 3), and it is proposed that this effect is mediated via different mechanisms that involve improvement of the general immune status of the blood, mobilization of immune cells and infiltration within the tumour

bed, and a shift towards a less immunosuppressive TME (51, 73, 82, 181). In addition, exercise may help to maintain a healthy immune system though its effects on the gut microbiome (25).

*I. Improvement of general immune status.*
Several forms of T cell dysfunction—anergy, exhaustion, and senescence—have all been reported in the cancer microenvironment, and it is a hallmark of inadequate anti-tumor immune responses (43). Regular exercise appears to reduce T cell dysfunction and to preserve or increase the frequency of naïve T cell populations (73).

Anergic T cells arise due to the absence of a costimulatory signal from dendritic cells because of the competitive binding of CTLA-4 expressed on Tregs to CD80 and CD86 on dendritic cells (36, 43). In animal studies, exercise interventions have been shown to reduce the tumour tissue expression of the Treg marker foxp3 (74, 111) (Table 3). In humans, observational studies show lower frequencies of Tregs in physically active people compared to people who were not involved in regular exercise (49, 76). Hence, decreasing the number of Tregs in the TME by exercise may reduce in turn the number of anergic T cells.

Senescent T cells appear with aging, due in part to thymic atrophy that reduces naïve T cell output, and to the exposure to various pathogens during life (21, 49, 129, 148). Based on a recent systematic review, Donovan et al. (47) concluded that acute exercise induces the mobilization of senescent CD8+ T cells into peripheral blood, and a tendency towards a decreased production/accumulation of senescent CD8+ T cells induced by increased cardiorespiratory fitness (47). Moreover, in sedentary adults over 65 years old resistance training interventions also appear to reduce the number of senescent CD8+ T cells (47), and those who are physically active have lower number of senescent CD4+ T cells than their inactive counterparts (72). Nevertheless, it should be noted that this review by Donovan et al. (47) only included studies in healthy populations which had several limitations such as small sample size and differences in immunophenotyping strategies. As such, the effects of exercise training on features of immunosenescence, remains unclear, as summarised recently elsewhere (51). Moreover, a key limitation of studies in the field is that T cells previously considered to be senescent (e.g., via CD27-, CD28-, CD57+, KLRG1+) expression may in fact be highly differentiated T cells that retain proliferative and effector functionality. Indeed, effector memory T cells with a highly differentiated, late/terminally differentiated phenotype share several features with senescent cells, such as shorter telomers, accumulated DNA damage and metabolic changes, but they retain proliferation capacities and effector functions under certain circumstances, as opposed to senescent T cells (127). Therefore, further studies are needed to elucidate the effects of regular exercise on truly senescent cells by combining several markers of T cell senescence and markers of cellular senescence (127).

Exhausted T cells, which upregulate PD-1 and other co-inhibitory receptors such as CTLA-4 (46), appear due to the action of inflammatory cytokines and to a prolonged stimulation of T cells, which progressively inhibits T cell effector functions (46, 47). Of note, this dysfunctional state is not irreversible, as blocking PD-1 or CTLA-4 with immunotherapy can restore CD8+ T cell-mediated immunity directly, and via depletion of CTLA-4 expressing regulatory T cells in the case of anti-CTLA-4 drugs (134, 173) . In healthy adults, acute exercise has been shown to induce the mobilization of PD-1+ exhausted CD8+ T cells into the peripheral blood compartment, however, acute exercise did not change the levels of CTLA-4+ CD8+ T cells (47). Conversely, having a sedentary lifestyle may increase the frequency of exhausted CD8+ T cells compared to physically active people (47). In early prostate cancer, a recent study showed that an acute bout of exercise on a cycling ergometer preferentially mobilized CD8+ T cells with the inhibitory receptor TIGIT, associated with T cell exhaustion introducing the concept that immunotherapy could synergize with exercise by reactivating mobilized but exhausted T-cells (141). Nevertheless, whether such changes correspond to an altered immunophenotype in the tumour remains unknown. We also note that PD-1 is transiently expressed upon T-cell receptor-mediated activation, and thus the sole expression of this inhibitory receptor may be insufficient to differentiate between exhausted and activated T cells (146, 173). Therefore, future studies should include a more comprehensive panel of markers to evaluate if exercise can mobilize bona fide exhausted T cells and prevent their accumulation, and moreover, understand whether exercise can alter immunophenotypes in the tumour microenvironment.

Mobilized T cells extravasate from the blood to peripheral and / or inflamed tissues after exercise, and it is thought that T cells are then exposed to a variety of pro-apoptotic stimuli (e.g., reactive oxygen species, glucocorticoids, cytokines) that may cause apoptosis of these cells (114, 147). If senescent and exhausted T cells are preferentially mobilized during exercise, they would be more exposed to apoptosis (47, 129, 147).. It is hypothesized that the removal of lymphocytes, and specifically senescent T cells, would create “immune space” to produce or maintain naïve T cells (47, 147), which would ensure an adequate immune response to detect newly encountered pathogens and novel cancer neoantigens (172). In a study by Mooren & Krüger (115), the injection of apoptotic CD3+ cells or the supernatant from these cells in untrained mice led to the mobilization of hematopoietic progenitor cells into the blood, which can differentiate into lymphocytes, which provides some support for parts of the immune space hypothesis. Two cross-sectional studies reported an increased frequency of naïve T cells, with higher number of both naïve CD8+T and CD4+ T cells in highly physically active adults (males cycling 100 km and females 60 km at least twice in the 3 weeks prior to testing) compared to non-active people of the same age group (49), and higher number of naïve CD8+T cells in subjects with higher aerobic fitness, indicated by estimated VO2max, as compared to less aerobically fit people (148). Similarly, both a concentric and eccentric endurance intervention (uphill and downhill walking) increased the frequency of naïve CD8+ T cells in pre-diabetic subjects (129). Nevertheless, a recent RCT in middle aged/older women at high risk of breast cancer showed that the number of CD4+ naïve T-cells and CD4+ recent thymic emigrants (the youngest subset of naïve T cells) decreased after a 12-week high intensity interval exercise program, whereas in patients who followed a moderate intensity interval exercise program there was no statistically significant difference in the frequency of these cells (123). Of note, some limitations to the immune space hypothesis have been proposed, including the proposal that there is a fixed

number of T cells, whether truly senescent/exhausted T cells versus highly differentiated T cells are eliminated by apoptosis, and whether it is advantageous depleting these cells instead of restoring their functions (51, 163). Indeed, highly differentiated T cells, among which some may be senescent and exhausted T cells, are necessary to control persistent virus (163). However, the removal of senescent cells that accumulate in tissues and organs due to aging can delay age-related pathologies (10) and, therefore, future studies analysing the effects of exercise and able to distinguish senescent and highly differentiated T cells, should evaluate if removing senescent T cells has benefits in the cancer setting.

Higher frequencies of naïve T cells found in physically active people may also be due to IL-7 and IL-15, which are both highly secreted by exercising muscles (49, 51, 73). These cytokines maintain naïve T-cell populations by promoting their survival and expansion in the periphery (73, 169). In addition, IL-7 and IL-15 sustain the survival of memory T cells (73, 150) which provide a better antitumor protection than late differentiated effector T cells (109). Furthermore, they promote the induction and expansion of stem cell memory T cells (51, 73, 108), which are more persistent and effective against tumours than central memory T cells (69). IL-7 treatment prevents CD27 and CD28 loss, which is a marker of T cell senescence, and maintains proliferative capacity and IL-2 production in human T cells co-cultured with tumor cells (73). IL-15 also promotes the differentiation and proliferation of NK cells (150) and the differentiation of T cells into resident memory T cells, which are thought to protect against tumour relapse and enhance therapeutic outcomes (110). In an orthotopic pancreatic ductal adenocarcinoma model, low-intensity treadmill-running has been reported to inhibit tumour growth by enhancing the infiltration of CD8+ T cells, while blocking IL-15 signalling reversed the exercise-mediated tumour protection and the influx of IL15Rα+ CD8 T cells into the tumour (99). Therefore, higher levels of IL-7 and IL-15 induced by exercise may promote the generation or maintenance of different subsets of T cells and NK cells, improving the host immune antitumoral response.

*II. Mobilization and infiltration of immune cells within the tumour.*

An acute bout of exercise leads to a rapid increase of immune cells in the blood, which is dependent on the haemodynamic shear stress and epinephrine-mediated stimulation of beta-2-adrenergic receptors on the surface of lymphocytes (6, 93). It is hypothesized that their distribution into peripheral tissues, especially NK cells and CD8+ T cells with a more potent effector phenotype, contribute to an enhanced immune surveillance (17, 21, 97, 181).

Exercise induces normalization of the tumour vasculature (6, 14, 112), which together with release of IL-6 from exercising muscles, promotes the upregulation of adhesion molecules on tumour vascular endothelium, facilitating the infiltration of immune cells into the tumour (6, 181). In healthy humans, acute exercise mobilizes mature and cytotoxic NK cells (17, 20) and enhances their cytolytic activity (136). In mice, Pedersen et al. showed that exercise decreased the incidence and tumor growth in a transplantable mouse model of melanoma and increased the number of NK cells infiltrated in the tumors as compared to non-exercised mice (128) (Table 3). Moreover, this effect was dependent on the release of epinephrine and IL-6 during exercise (128). Interestingly, tumors were smaller in wild type exercised mice than in athymic exercised ones, implying that T cells also mediated the exercise-induced antitumoral effect, and that the lack of T cells failed to control the growth of small tumours (128). They also showed that exercised mice had higher infiltration of dendritic cells in the tumours than control mice (128), which are necessary for the priming and activation of CD8+T cells (96). Other preclinical training studies have reported that exercise augments dendritic cell numbers and promotes their maturation and function (16, 29) (Table 3). Therefore, exercise may also promote an adaptive immune antitumoral response via increased number and function of dendritic cells.

Several studies in mice have confirmed the involvement of CD8+T cells in the antitumoral effects of exercise (70, 74, 99, 137) (Table 3). Thus, exercise modulates their mobilization and tumour infiltration through different mechanisms, such as maintenance of the gradient of the lipid mediator sphingosine 1-phosphate between blood, lymph, and tissues (99). This gradient is necessary for the trafficking of lymphocytes and for promoting an appropriate population of circulating lymphocytes (160) Another mechanism by which exercise induces the mobilization of CD8+ T cells is the loss of surface expression homing markers caused by increases in of tricarboxylic acid cycle metabolites and lactate in blood and secondary lymphoid organs (137). Finally, exercise can increase their recruitment into tumours via chemokine signalling the tumours (70).

*III. Decreased local immunosuppression.*

Exercise can ameliorate immunosuppressive conditions in the TME such as hypoxia, high lactate concentrations with consequent acidity, and increased inflammatory mediators thereby promoting antitumor immunity (6, 51, 93, 181). Exercise increases tumoral blood flow by improving tumour microvessel density and maturity (6, 14, 112), which reduces tumor hypoxia (6, 14, 112). Moreover, in breast cancer bearing mice, endurance training decreased tumour volume and modulated the expression of enzymes involved in lactate metabolism, resulting in decreased lactate in the tumour, which may reduce acidification of the TME (7). Reducing acidity in the TME would contribute to an antitumoral immunity, as an acidic tumour microenvironment impairs T cell and NK cell function (6, 110, 181). Inflammatory inhibitors of T cells such as IL-10 and TGF-beta are released by tumour cells and immunosuppressive cells (100). Exercise in mice has been reported to reduce tumor growth together with a reduced infiltration of innate and adaptive immune cells associated with an immunosuppressive microenvironment, such as macrophages (174, 183), neutrophils (99, 174, 183), MDSCs (66, 99, 171) and Tregs (74, 111) (Table 3). Furthermore, there is some preclinical evidence that exercise can promote polarization towards an anti-tumoral M1 subtype in macrophages isolated from the peritoneum (1, 119), and decrease the pro-tumoral M2 subtype polarization amongst tumour associated macrophages (90, 111) (Table 3). However, the effects of exercise on the polarization of neutrophils have not been assessed (149).

Exercise-induced reductions in hypoxia and acidity, a reduction to immunosuppressive cells and a higher infiltration and competency of antitumour T cells could theoretically increase the number of dead tumor cells, in turn reducing the

immunosuppressive conditions in the TME (51, 83, 178, 181). Preclinical studies have assessed gene expression profiling within the TME, showing that exercise interventions in different cancer models induce a more pronounced antitumoral immune environment, with upregulation of oxidative metabolism (70), increases in NK cell (128) and CD8+ T cell (88) markers, and a downregulation of several pathways involved with immunosuppression (70) (Table 3).

*IV. Modulation of the microbiome*

In murine models, running has been reported to induce changes in the composition and function of the microbiota, with an increased alpha diversity, a measure of microbial diversity, within a sample, and associated with a higher response to cancer treatments (78), more butyrate-producing taxa and an increase in the production of SCFAs (4, 32, 168). Some cross-sectional studies in athletes have also reported that exercise influences the microbiome, increasing microbial diversity and the number of butyrate producing species and species associated with improved metabolic health (31, 88). Moreover, cardiorespiratory fitness is a predictor of microbial diversity and production of butyrate in healthy humans (32, 52). Regarding longitudinal exercise training effects, in sedentary subjects with insulin resistance, both sprint interval running, and moderate-intensity continuous training modified microbiota profile by increasing the Bacteroidetes phylum and decreasing the Firmicutes/Bacteroidetes ratio, and also decreasing systemic and intestinal inflammatory biomarkers (117). Similarly, in unfit volunteers, exercise interventions have been reported to significantly increase microbial diversity (11), Akkermansia abundance (118), and butyrate-producing taxa and SCFAs (4). Conducting faecal transplants from a breast cancer survivor who underwent an exercise intervention into germ-free cancer-bearing mice that did not undergo any exercise training resulted in smaller tumour volume in those mice who received post exercise faecal samples compared to those receiving pre-exercise samples, demonstrating that exercise may have antitumor activity through an effect only mediated by the gut microbiome (139). Nevertheless, in cancer patients, the effects of exercise on gut microbiome remains unexplored, especially in terms of treatment efficacy (168). An ongoing RCT in patients with prostate cancer receiving androgen deprivation therapy will assess the impact of a supervised exercise program on gut microbiota (121).

**Synergy between exercise and chemotherapy**

Exercise can synergize with chemotherapeutics in several ways (6, 30, 179). First, exercise may limit chemotherapy toxicity in highly perfused organs such as brain, bone marrow, heart, lungs and kidneys by increasing the blood perfusion in muscles, and hence, the volume for chemotherapy distribution. (30). Second, exercise-induced increase of blood irrigation helps to deliver drugs to tumours (6). Indeed, Betof et al. demonstrated that exercise improved tumour perfusion, reduced hypoxia, and also increased the effectiveness of cyclophosphamide chemotherapy, delaying tumour growth in two orthotopic models of murine breast cancer (14). Similarly, in murine models of pancreatic ductal adenocarcinoma (56, 140), melanoma (140) and Ewing sarcoma (116), gemcitabine and doxorubicin were significantly more efficacious at reducing cancer burden in exercised mice due to the exercised-induced normalization of tumour vasculature. Interestingly, cyclophosphamide, gemcitabine and doxorubicin are considered ICD inducers. Although the antitumoral effects of exercise through immune mechanisms were not assessed, it may be the case that ICD was enhanced by chemotherapy in these studies. Considering hypoxia, this reduces the expression of MHC- I in tumour cells (6, 145), which would impede the ability of CD8+T cells to recognize tumour cells (6, 61, 145). Moreover, hypoxia inhibits antigen uptake by dendritic cells (50) and limits their maturation and activity, preventing them from priming naïve T cells (170). Therefore, by relieving hypoxic conditions with exercise, the antigenicity of tumor cells succumbing to chemotherapy-induced ICD and the activity of dendritic cells may be enhanced, enabling CD8+ T cell function. Furthermore, because the adaptive immune response triggered by ICD can only be executed if the TME conditions are favorable for the infiltration and function of T cells (63, 95), exercise may have a synergistic effect by increasing the infiltration of T cells and reducing immunosuppressive conditions in the TME. It should be noted, however, that some of the mentioned studies used nude mice (56, 116), which lack T cells. Nevertheless, they have an innate system and so exercise-induced increased infiltration of NK cells may synergize with ICD inducers as they can modify the tumor surface phenotype and sensitize them to NK cells-mediated killing (53).

**Exercise interventions in clinical trials in cancer patients**

The safety and feasibility of exercise during and after anti-cancer treatment across several cancers, disease stages and treatment regimens has been established. Additionally, beneficial effects on improvement in body composition, cardiovascular fitness, muscle strength, physical function, and psychosocial outcomes, and reduced treatment-related adverse effects are well documented (30, 89, 102, 175). However, little is currently known about the effects of exercise on immune parameters in cancer patients (Table 4). In a recently published clinical trial in patients with oesophageal cancer undergoing neoadjuvant chemotherapy, the exercise group (combined aerobic and strength training) had higher rates of tumour regression compared to the control group (75% vs 36.8%, p=0.025), and differentially regulated immunity and inflammatory markers, with higher counts of CD3+ and CD8+ T cells (188). Similarly, a pre-surgical aerobic and strength training intervention in breast cancer patients resulted in upregulation of pathways related to immune cell function and inflammatory signaling and a trend towards a decreased expression of Foxp3 within the TME although patient outcomes have not been reported (103).

Recently, patients with pancreatic adenocarcinoma who underwent exercise concurrent with neoadjuvant chemotherapy or chemoradiation prior to surgical resection in a prospective clinical trial, had a higher number of infiltrating CD8+ T cells and a trend toward higher expression of granzyme B compared with matched historical controls (99). Notably, patients who had a higher number of CD8+ T cells or granzyme B in the tumour had higher median overall survivals (p=0.01 and 0.04 respectively) (99). In a 12-week intervention of supervised aerobic training (cycle ergometry) in patients with eight different solid tumours receiving cytotoxic therapy and synthetic erythropoietin, those exercising showed a trend towards an increased number of total circulating CD8+ T cells and CD8+CD45RA+ T cells, compared to patients receiving usual care, together with decreases to pro-inflammatory cytokines and angiogenic factors in their blood (68).

Moreover, there is evidence of enhanced NK cells activity after exercise interventions (54, 98, 126, 141, 161). Thus, an increment has been reported after a single bout of acute exercise in prostate cancer patients scheduled to undergo prostatectomy (141), after a 15-week aerobic exercise intervention in post-menopausal breast cancer survivors (54), and after 9-12 weeks of aerobic and resistance training during (neo)adjuvant chemotherapy in breast and colon cancer patients (161). Moreover, exercise modified the expression of NK receptors, with a decreased expression of the inhibiting receptor KIR2DL1 (126) and an increased expression of the activating receptors NKG2D (126) and NKp46 (161), suggesting a higher cytotoxic potential (126, 161). Regarding the infiltration of NK cells in cancer patients, two recent randomized controlled trial in men with localized prostate cancer have been conducted. Schenk et al., showed that after an acute bout of aerobic exercise on the day before surgery, there were not differences in NK cell infiltrates in the tumor tissue between the exercise and the control group (142). The other RCT used a preoperative aerobic high intensity interval training four-times per week from time of inclusion until scheduled surgery. It was reported that there was a within-group increase in tumour NK cells in the exercise group, and a between-group difference in healthy prostatic tissue, though NK cell frequency was low (45, 64). Nevertheless, the study did not show a difference in the number of infiltrating NK cells in the tumours from baseline to follow-up between groups, neither with the intention-to-treat nor the per-protocol analysis.

Regarding disease outcomes in observational studies, a recent prospective cohort study of 1,340 breast cancer patients concluded that meeting the minimum guidelines for physical activity, defined as the MET hour equivalent of 150 minutes of moderate-intensity regular physical activity per week, before and after chemotherapy treatment significantly reduced the risk of cancer recurrence and mortality (23). Moreover, a systematic review and meta-analysis found improved survival with higher prediagnosis or postdiagnosis levels of physical activity for 11 cancer types (59). Similarly, overall mortality was significantly reduced by a higher level of physical activity in the 8 non-randomised trials in patients with advanced cancer (breast, colorectal, lung and brain) included in a systematic review and meta-analyses (156). Regarding intervention studies, a recent systematic review of exercise interventions during neoadjuvant, primary, and adjuvant therapy reported an enhancement of the efficacy of cancer therapies although the studies included were not designed for this purpose (179). Three ongoing large multicenter randomized trials are evaluating if targeted exercise improves clinical outcomes including progression free and overall survival in colonic, prostate and hematological malignancies (35, 122, 176).

## COMBINING FASTING AND EXERCISE INTERVENTIONS

Combining fasting or caloric restriction with endurance training has been reported to have synergistic effects in a non-cancer population, with attenuation of muscle autophagy and increase in muscle repair, as well as metabolic changes (87). In the cancer setting, work to date has focused on targeting single molecules within an individual regulatory network; however, complementary strategies able to act on multiple higher order networks can be a more effective therapeutic approach (94) . Similarly, immune-oncology has aimed mainly to act on the TME, yet immunity is coordinated across multiple tissues (79). Thus, therapeutic interventions that include both fasting and exercise interventions, which are able to target multiple systemic responses, may be a useful strategy to supplement chemotherapy with synergistic or additive effects.

Although scarce, some preclinical studies have shown positive results in cancer models (Table 5). Using a skin tumor-sensitive murine model for enhanced susceptibility to TPA-promoted skin carcinogenesis, Xie et al. demonstrated that a 20% reduction in calories was sufficient to decrease PI3K and Ras pathways, but only when combined with treadmill exercise training was there a significant increase in caspase-3-like proteolytic activity in tumours, suggesting an apoptosis-mediated mechanism (177). In a metastatic model of breast cancer, voluntary wheel running combined with a 10% reduction in calories compared to control mice was shown to delay tumour growth, metastatic progression, and improve survival, as compared to either intervention alone (162). Additionally, the combination reduced the expression of metastatic and immunosuppressive genes and increased the CD8+ T cell/MDSC ratio in the tumour (162). Furthermore, adding caloric restriction to wheel running in mice further protected from the cardiotoxicity induced by doxorubicin, a chemotherapeutic used for the treatment of a variety of cancers (75).

Regarding human studies, there are a few promising reports regarding feasibility, patient-related and therapeutic outcomes (Table 5). One proof-of-concept case study utilized a fasting and exercise intervention in a woman with recurrent stage III ovarian cancer, during a 3-day period once a month over the course of 3 consecutive months (3). There were improvements in physical and psychological symptoms, and the participant adopted positive lifestyle modifications. A randomized controlled trial compared intermittent energy restriction vs continuous energy restriction for weight control throughout the 4.5–6-month course of adjuvant/neoadjuvant chemotherapy in early breast cancer patients. The intermittent energy restricted diet consisted of two consecutive low-energy, low-carbohydrate days, which provided 650–1000 kcal, immediately prior to chemotherapy infusion; for the other five days of the week patients were recommended to follow a Mediterranean diet, which was tailored so that overall weekly intake matched their energy requirements for weight loss or maintenance. The continuous energy restricted diet was a Mediterranean diet every day of the week tailored to their energy requirements for weight loss or maintenance. This trial also included exercise recommendations for both intervention arms (77). Exercise levels did not increase in either group as compared to baseline levels, but it was maintained at 3 weeks post chemotherapy, as opposed to the previously reported 20% decrease in physical activity alongside chemotherapy in these patients (77). A prospective, non-randomized, controlled trial designed to decrease fat gain during the 4 weeks of induction chemotherapy in adolescent patients with acute lymphoblastic leukaemia using a caloric deficit of ≥10% and a home-based exercise intervention combining aerobic + resistance training,

significantly reduced minimal residual burden risk compared to historical controls (125). Although adherence to the prescribed exercise was only 31%, lean mass loss was similar to that found in historical controls, indicating that caloric restriction did not worsen the loss of lean tissue (125).

## LIMITATIONS AND CHALLENGES OF DIETARY RESTRICTION AND EXERCISE INTERVENTIONS

Most of our knowledge of the effects of dietary restriction and exercise arise from preclinical data. However, the physiological, metabolic, immunological, and genetic differences between rodent models and humans, and the high diversity of cancers, treatments, and comorbidities in humans, challenges the translation of animal studies to humans. For example, the fasting timeframe shown to be beneficial in animal studies cannot be translated to humans, as mice have a much higher metabolic rate. Specifically, the equivalent of a 24h water only fasting in rodents would be equivalent to 5 days in humans (33). Similarly, there are knowledge gaps related to the role of the intensity, dose, and mode of exercise on the immunomodulatory aspects in preclinical studies, which makes it difficult to develop generalized exercise guidelines as cancer treatment. For example, different durations and intensity may impact the release of different myokines and promote differential shifts on the immune cell's phenotype. Therefore, while animal models provide valuable insights into biological mechanisms, the translation of findings to human populations requires careful consideration of the limitations mentioned above.

## CONCLUSION AND FUTURE DIRECTIONS

The efficacy of conventional chemotherapeutics greatly depends on the immunological competence of the host. Chemotherapy agents increase the immunogenicity of tumour cells by increasing the presentation of antigens on MHC-1 molecules and by inducing the release of molecules from dying tumour cells that unleash an adaptive immune response in the host against the tumour. This increased immunogenicity must be perceived by the immune system. However, because tumours evolve to evade recognition by immune cells, the functions of the antitumoral immune system are often compromised, reducing the efficacy of chemotherapy. We propose that interventions including both dietary restriction and exercise could be used as adjunct non-pharmacological approaches in clinical trials in cancer patients during chemotherapy treatment, as they could increase tumour response, while having no serious adverse events for cancer patients. Dietary restriction and exercise have the potential to each improve different subsets of immune populations at the systemic level and ameliorate the conditions within the TME towards a more tumour-suppressive and less immunosuppressive one, through overlapping but also through different pathways, eventually leading to enhanced therapeutic response.

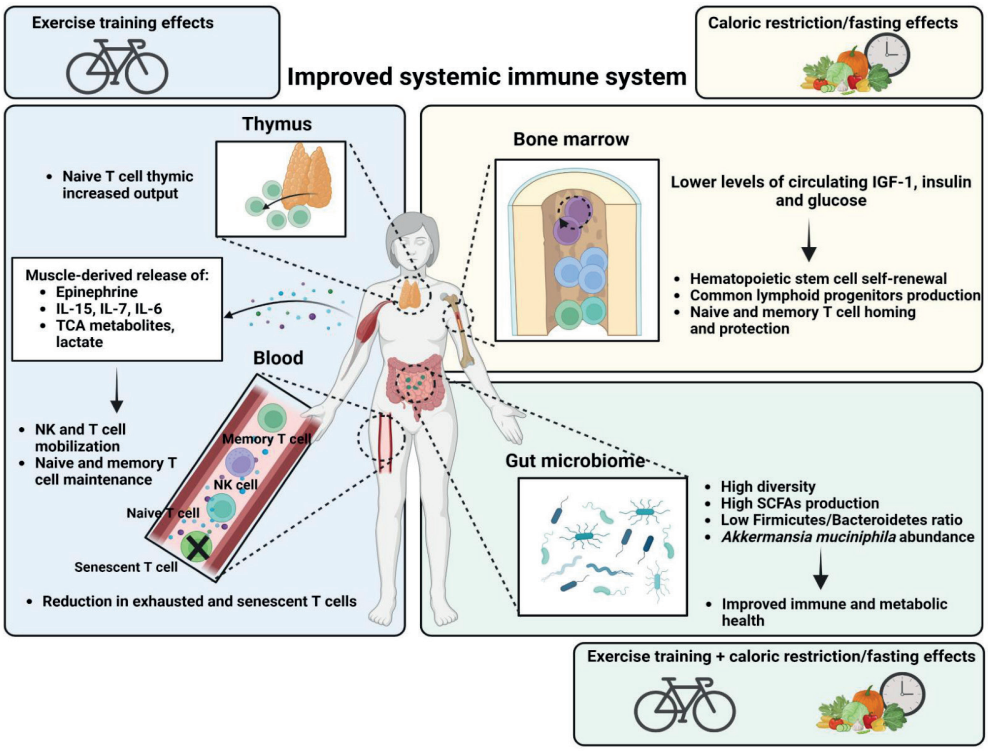


**Figure 1.** A synthesis of the systemic changes induced by caloric restriction/fasting and exercise. Caloric restriction/fasting decrease the availability of nutrients and growth factors, and this reduction leads to the protection of progenitors, naïve and memory T cells in the bone marrow. Conversely, exercise may decrease the number of circulating senescent and exhausted T cells, and in turn, increase the output of naïve T cells. Moreover, exercise can induce the maintenance and mobilization of antitumoral immune cells, increasing their ability to patrol peripheral tissues. Finally, caloric restriction, fasting and exercise may induce modifications in the gut microbiome that are related to improved metabolic and immune health.

At the systemic level, fasting regimens may improve the antitumoral immunity by enhancing hematopoietic stem cell regeneration, the production of common lymphoid progenitors in the bone marrow and by maintaining naïve and memory T cell populations. Similarly, exercise can enhance systemic immunity by decreasing dysfunctional T cells such as exhausted and senescent cells, while increasing the output of naïve T cells from the thymus, and the maintenance of naïve and memory T cells. Moreover, exercise also mobilizes T cells and NK cells, increasing their surveillance capability of peripheral tissues. Finally, both interventions may influence systemic innate and adaptive immune components by promoting beneficial shifts in the gut microbiota (Figure 1). At the local level, the immunogenicity (antigenicity and adjuvanticity) of tumour cells succumbing to ICD may be increased by both fasting-induced autophagy and exercise-induced reduced hypoxia. The increased immunogenicity of the dying tumour cells will increase their susceptibility to an immune attack, and this process starts with antigen uptake and maturation of dendritic cells. Exercise could support this part of the process by increasing the recruitment, function, and maturation of dendritic cells, which are then able to prime and activate naïve CD8+ T cells against tumour cells. Finally, dietary restriction and exercise interventions can help increase the infiltration of CD8+ T and NK cells within the TME and maintain their effector functions through the reduction of immunosuppressive conditions by decreasing the number of MDSCs, T regs and M2 macrophages, and reducing hypoxia and lactate concentration. A shift in the TME towards a more tumour-suppressive one would, in turn, increase the number of dying tumour cells, which would decrease the immunosuppressive factors released to the TME, further enabling immune cells competency against the tumour (Figure 2).

Supervised dietary restriction and exercise interventions could be implemented as part of the supportive care guidelines for cancer patients under chemotherapy treatment, as they are inexpensive, have low risks, and can decrease drug toxicity, improving quality of life. Although preclinical findings are that dietary restriction and exercise can increase the efficacy of chemotherapy, this remains unknown in humans. Adequately powered and carefully planned clinical trials are required to study the safety and efficacy of interventions using dietary restriction and exercise training during chemotherapy treatment, measuring response rates and survival outcomes. Furthermore, clinical trials should be designed to identify the most beneficial form of dietary restriction and exercise type and dosage to define standards of care. Finally, the biological mechanisms behind the effects of these interventions should also be further studied by including biological samples (e.g., tissue, serum or plasma, peripheral blood mononuclear cells) to address research gaps such as the impact on the release and exposure of DAMPs in tumour cells, composition and functions of the different circulating and tumour-infiltrating innate and adaptive immune cells, composition of the gut microbiota, and the genetic and epigenetic landscape of the tumours. Further, these phenomena should be tested for association with objective response measures (e.g., tumour size, pathological and radiological response in the neoadjuvant setting) and time to event outcomes (i.e., in the adjuvant setting).

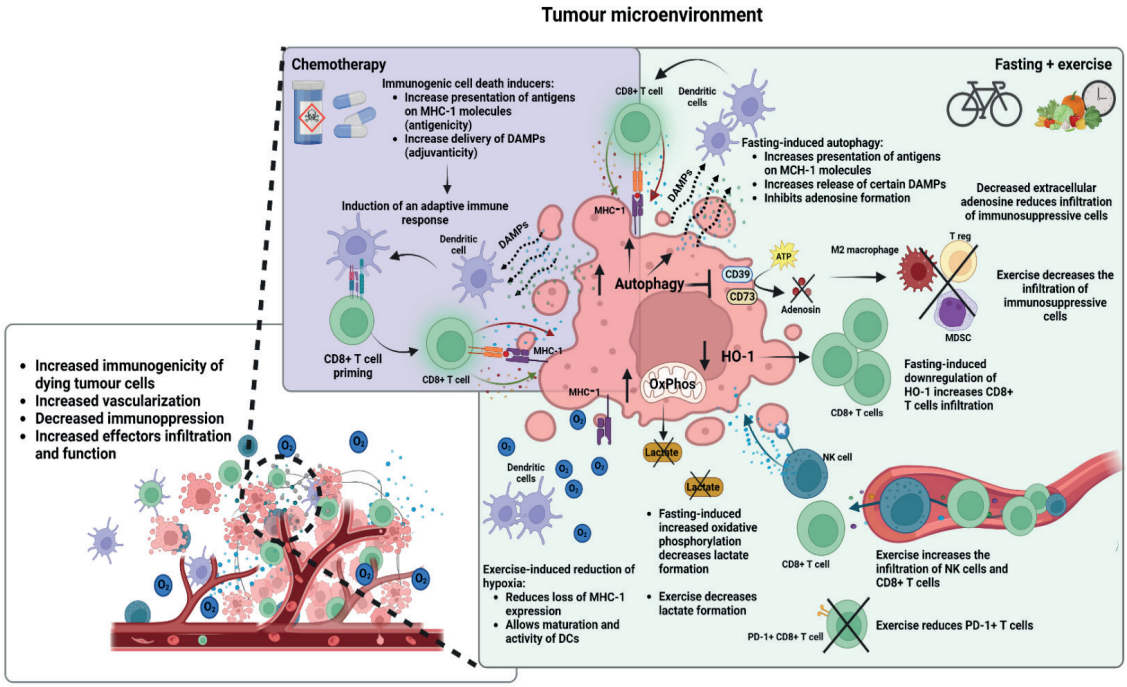


**Figure 2.** A synthesis of local changes promoted by caloric restriction, fasting and exercise. Tumour cells dying due to ICD inducers increase their antigenicity and their adjuvanticity, inducing an adaptive immune response against the tumour. Fasting and exercise may support antigenicity and adjuvanticity of tumour cells by promoting autophagy and relieving hypoxia, respectively. Fasting and exercise interventions may also promote a shift in the TME conditions into a more antitumoral and less immunosuppressive environment, reinforcing tumour cell death induced by chemotherapy. Thus, fasting may lead to an increased infiltration of CD+ T cells by downregulating the expression of HO-1, and to a decreased accumulation of immunosuppressive cells by decreasing adenosine production. Moreover, fasting increases oxidative phosphorylation in tumour cells, which decreases the production of lactate. Conversely, exercise increases the infiltration of CD8+ T cells and NK cells and it may reduce the number of exhausted T cells (PD-1+). Additionally, exercise can decrease immunosuppressive conditions by reducing the infiltration of immunosuppressive cells, decreasing hypoxia, and lowering lactate production by tumour cells.

**Table 1:** Overview of in vivo cancer models reporting immunomodulatory effects of caloric restriction/fasting

| **Table 1.** Overview of *in vivo* cancer models reporting immunomodulatory effects of caloric restriction/fasting. | | | |
|---|---|---|---|
| **Ref** | **Model** | **Intervention** | **Outcomes** |
| Di Biase et al., 2016. Ref (44) | • BALB/c (wild type) and BALB/c-nude mice C57BL/6 mice<br>• 4T1 murine breast cancer and B16 murine melanoma cells, implanted subcutaneously | • 4 days FMD. One FMD cycle every 2 weeks, after tumour implantation.<br>• 4 days FMD+ DXR or CP, 2 or 3 cycles every 2 weeks, after tumour implantation | • FMD alone retarded tumour growth and reduced IGF-1. Increased in CD8+ T cells in blood and common lymphoid progenitor cells in the bone marrow.<br>• FMD+ DXR or CP had the highest antitumoral effect.<br>• FMD + DXR increased CD8+ T cells and decreased Tregs in tumours. Required downregulation of HO-1 in tumour cells. |
| Pietrocola et al., 2016. Ref. (131) | • C57Bl/6, BALB/c, and nude athymic (nu/nu) mice, LSL-K-rasG12D; Atg5fl/fl; CD39+ mice<br>• MCA205 murine fibrosarcoma, TC-1 non-small cell lung, or CT26 colorectal cancer cells implanted subcutaneously | • 48 h STF, 1 cycle, + MTX or OX, after tumours became palpable.<br>• Caloric restriction mimetic: daily administration of hydroxycitrate (HC) | • STS + MTX or OX reduced tumour growth. Required immunocompetency and autophagy.<br>• HC+ MTX or OX reduced tumour growth. Required CD8+ T cells, autophagy, and extracellular ATP. Mediated by T regs depletion.<br>• HC induced autophagy in KRas-induced lung adenocarcinomas, and decreased tumour growth and the infiltration of Tregs. No effect of HC in autophagy deficient, T and B cells deficient or CD39 overexpressing transgenic mice. |
| Sun et al., 2017. Ref. (154) | • BALB/c mice<br>• CT26 colorectal cancer cells implanted subcutaneously.<br>• CT26 and RAW264.7 cells, in vitro | • Alternate day 24 h STF, 5-7 days after tumour implantation, for 2 weeks | • Suppression of tumour growth and M2 subtype polarization of macrophages.<br>• Mechanisms in vitro: suppression of M2 polarization, increased expression of autophagy genes, decreased expression of CD73 and decreased generation of adenosine. |
| Collins et al., 2019. Ref. (34) | • C57BL/6 mice<br>• Virally induced transgenic CD8+ pmel-1 cells against the melanoma epitope gp-100.<br>• B16 melanoma cells, implanted subcutaneously | • Daily 50 % CR for 3 weeks, before tumour implantation | • Memory T cells reversely accumulated within the bone marrow.<br>• Enhanced protective function of memory T cells against melanoma tumours, increasing mice survival. |

| | | | |
|---|---|---|---|
| | • B16 melanoma cells, implanted subcutaneously | | |
| Ajona et al., 2020. Ref (2) | • Sv/129 and C57BL/6J mice<br>• 393P or LLC lung tumour cells implanted subcutaneously | • 48 h STF, 3 cycles + anti-PD-1 therapy, 6 days after tumour implantation | • Inhibition of cancer progression and increased survival.<br>• Increased tumour infiltration of NK and CD8+ T cells and decreased number of Tregs.<br>• Decreased IGF-1–IGF-1R signalling in tumour cells. |
| Pomatto -Watson et al., 2021. Ref. (133) | • BALB/c mice<br>• 4T1 murine breast cancer cells implanted subcutaneously | • 4:10 cycles: 4 days FMD (50% reduced on first day, 70% reduced on days 2-4) or 4 days of CR diet (50% reduced on first day, 70% reduced on days 2-4), followed by 10 days *ad libitum*, 7 days after tumour implantation (Post) or 21 days before tumour implantation (Pre).<br>• Daily 20% CR, 7 days after tumour implantation (Post) or 21 days before tumour implantation (Pre). | • All interventions delayed tumour growth compared to ad libitum mice.<br>• Higher effect of daily CR (pre ad post) over 4:10 cycles diets.<br>• Daily CR reduced metastasis in lungs.<br>• Reduced number of Tregs in blood in daily CR and 4:10 cycles FMD and CR, compared to *ad libitum* mice.<br>• Reduced number of MDSCs in spleen in daily CR mice, and reduction in tumours in FMD and daily CR mice.<br>• Increased number of effector CD8+ and CD4+ cells in blood and spleens in daily CR mice.<br>• Reduction in total MDSCs in tumours in FMD and daily CR mice. |
| Fu et al., 2021. Ref. (60) | • BALB/c mice<br>• 4T1 and 4T07 murine breast cancer cells implanted subcutaneously | • 48 h STF, 2 cycles, +/-DOC, 14 days after tumour implantation. | • STS suppressed of tumour growth as efficiently as DOC.<br>• STS inhibited splenic accumulation of CD205+ G-MDSCs by attenuating cell trafficking and inducing apoptosis trough inhibition of glucose metabolism. |

[1] STF: short-term fasting. FMD: fasting mimicking diet. CR: caloric restriction. DXR: Doxorubicin. CP: cyclophosphamide. DOC: docetaxel. MTX: Methotrexate: MTX. OX: Oxaliplatin. HO-1: heme oxygenase-1. IGF-1: insulin growth factor 1. MDSCs: myeloid-derived suppressor cells. Tregs: regulatory T cells.

**Table 2:** Overview of clinical studies reporting immunomodulatory effects of fasting in in cancer patients

| Ref | Cancer type | N | Intervention | Outcomes |
|---|---|---|---|---|
| De Groot et al., 2015. Ref. (39) | Breast cancer | 13 | • STF (0 kcal) 24 h before and 24 h after CT. 6 cycles.<br>• Control arm: regular diet | • Decreased IGF-1.<br>• Higher erythrocyte and thrombocyte numbers.<br>• Reduced DNA damage in PBMCs. |
| Dorff et al., 2016. Ref. (48) | Distinct cancers | 20 | • STF (<200 kcal per day) 24 h, 48 h prior CT or 72 h (divided to 48 h prior to and 24 h post chemotherapy). 2 cycles maximum. | • Decreased IGF-1 by 30, 33 and 8 % in the 24, 48 and 72 h fasting cohorts, respectively.<br>• Reduced DNA damage in PBMCs when fasting ≥48 h. |
| De Groot et al., 2020. Ref. (37) | Breast cancer | 129 | • FMD, 5 days, 3 days prior and on same day of NACT. 8 cycles.<br>• Control arm: regular diet | • FMD arm did not receive dexamethasone.<br>• Increased rate of radiologically response and pathological response. in ITT and PP analysis, respectively<br>• Reduced DNA damage in PBMCs. |
| Vernieri et al., 2022. Ref. (167) | Distinct cancers | 95 | • FMD, 5 days, + standard antitumor therapies. 8 cycles.<br>• Pre versus post intervention. | • Reduced glucose, insulin, and IGF-1.<br>• Decreased immunosuppressive myeloid cells and Treg cells.<br>• Increase of NK and CD8+T cells with an activated phenotype. |
| Vernieri et al., 2022. Ref. (167) | Invasive breast cancer | 100 | • FMD, 5 days, 1 cycle, 7-10 days before surgery, without treatments.<br>• Pre versus post intervention | Preliminary data in breast cancer patients:<br>-<u>In tumours</u><br>• Decreased IGF-1R and p-IGF-1R.<br>• Increased CD8+ T cells infiltration and CD8/CD68+ ratio.<br>• Increased expression markers of NKT, activated dendritic cells, central and effector memory CD4+ and CD8+ T cells and M1 subtype macrophages, and no change in M2 subtype.<br>-<u>In PBMCs:</u><br>• Increase of DCs, NK cells, B cells and several subsets of memory T cells and reduction of exhausted and hyperexhausted T cells, Tregs, and MDSCs. |

[2] STF: short-term fasting. FMD: fasting mimicking diet. CT: chemotherapy. NACT: neoadjuvant chemotherapy. PBMCs: peripheral blood mononuclear cells. DCs: dendritic cells. NKT cells: natural killer T cells. MDSCs: myeloid derived suppressor cells. Tregs: regulatory T cells. ITT: intention to treat. PP: per protocol. IGF-1: insulin growth factor 1. IGF-1R: insulin growth factor 1 receptor. p-IGF-1R: phosphorylated insulin growth factor 1 receptor.

**Table 3:** Overview of in vivo cancer models reporting immunomodulatory effects of exercise

| Ref | Model | Intervention | Outcomes |
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| Zielinski et al., 2004. Ref. (183) | • BALB/cByJ mice<br>• EL-4 lymphoma cells implanted subcutaneously. | Treadmill running, high intensity, 3 h/day or until volitional fatigue, daily. Starting immediately before tumour inoculation. | • Delayed tumour growth.<br>• Reduced macrophages and neutrophils infiltration (determined by hematoxylin-eosin histological analysis). |
| Murphy et al., 2004. Ref. (119) | • C57BL/6 mice<br>• B16 melanoma cells implanted intravenously. | Treadmill running, 1 h/day, for 6 days. With or without oat fibre beta-glucan.<br>Tumour inoculation 30 min after the last day of exercise. | • Decreased number of tumour foci at lungs in all groups compared to non-exercised non-beta glucan group.<br>• Increased macrophages cytotoxicity against B16 cells *in vitro* compared to non-exercised non-beta glucan group. |
| William et al., 2009. Ref. (174) | • Swiss mice<br>• Ehrlich tumour cells implanted subcutaneously. | Swimming, at 50% or 80% of maximal weight, 1 h/day, 5 days/week for 6 weeks. Starting 4 weeks before tumour inoculation. | • Reduced tumour growth at 50% of maximal workload.<br>• Reduced macrophages and neutrophils infiltration (determined by N-acetylglucosaminidase and myeloperoxidase activity, respectively). |
| McClellan et al., 2014. Ref. (111) | C57BL/6 ApcMin/+ mice | Treadmill running. 1 h/day, 6 days /week from 4 to 16 weeks of age. | • No effect of exercise on polyp's number.<br>• Reduction in the number of large polyps.<br>• In mucosal tissue, decreased expression of general macrophage marker, M2 macrophage markers and Foxp3, increased expression of CD8. |
| Abdalla et al., 2014. Ref. (1) | • Balb/c mice<br>• Breast tumours induced by7,12-dimethylbenzanthracene. | Swimming, 5 days/week for 8 weeks. | • M1 profile of peritoneal isolated macrophages (higher secretion of IFN-γ, TNF-α and IL-12). |
| Pedersen et al., 2016. Ref. (128) | • C57BL/6 mice<br>• B16F10 melanoma or<br>• Lewis's lung cells implanted subcutaneously or intravenously.<br>• DEN-induced liver tumours<br>• Transgenic (Grm1) EPv transgenic mice as melanoma model | Voluntary wheel running.<br>4 weeks before and/or after tumour inoculation. | • Reduced tumour growth/incidence and reduced lung metastases. In Tg(Grm1)EPv transgenic a trend to delayed tumour formation.<br>• Upregulation of immune-related pathways in B16 tumours.<br>• Increased NK, CD3+ and dendritic cells in B16 tumours.<br>• Antitumor effects of exercise in B16 model suppressed by blockade of b-adrenergic signalling and anti-IL-6 antibody. |

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| Bianco et al., 2017. Ref. (16) | • Balb/c mice<br>• 4T1 murine breast cancer cell line implanted orthotopically. | Swimming, 5 days/week for 4 weeks, progressing from 30 to 45 min /day. Starting with one week of adaptation (15 min) when tumour inoculation. | • Reduced tumour growth.<br>• Trend to increased infiltration of CD8+ T cells.<br>• Increased number of differentiated bone marrow-derived DCs and expression of DC costimulatory CD80 and CD86 in tumours. |
| Hagar et al., 2019. Ref. (74) | • BALB/c wild type and nude (athymic)<br>• 4T1 murine breast cancer cell line, implanted subcutaneously. | Treadmill running, increasing velocity up to 26 min/day, 5 days/week, for 8 weeks. Tumour inoculation 72 h after exercise intervention | • Reduced tumour growth and increased survival.<br>• Increased total white blood cells.<br>• Reduced FoxP3+Tregs in tumours.<br>• No effect of exercise on tumour growth in athymic mice. |
| Rundqvist et al., 2020. Ref. (137) | • FVB mice<br>• I3TC murine breast cancer cell line, implanted subcutaneously. | Voluntary wheel-running, 14 days prior to and after tumour inoculation, until end of experiment. | • Reduced tumour growth and increased survival.<br>• Increased infiltration of CD8+ T cells in tumours, spleens, and tumour-draining lymph nodes.<br>• Increased lactate and TCA cycle metabolites in plasma and secondary lymphoid organs.<br>• Lactate and TCA cycle metabolites induced loss of CD62L in CD8+T cells *in vitro.*<br>• Lactate increased Granzyme B expression in CD8+ T cells and cytotoxicity *in vitro.*<br>• CD8+ T cells from trained mice transferred to tumour-bearing untrained animals increased survival and reduced rate of tumour growth, when compared to animals receiving CD8+ T cells from non-trained animals. |
| Wennerberg et al., 2020. Ref. (171) | • BALB/c mice<br>• 4T1 murine breast cancer cell line, implanted subcutaneously. | Treadmill running, 30 min/day, 5 days/week, 8 days after tumour inoculation, until end of experiment. | • Reduced tumour growth.<br>• Reduced number of MDSCs in spleens and tumours.<br>• Increased Ki-67 and CD69 expression in NK cells in spleens.<br>• Increased CD69 expression in CD8+T cells in tumours. |
| Garritsoni et al., 2020. Ref. (66) | • BALB/c mice<br>• 4T1 murine breast cancer cell line implanted orthotopically. | Voluntary wheel running. Starting 6 weeks before tumour inoculation, and continued 6,20,24, and 28 days post-tumour injection. | • Reduced number of MDSCs in spleen, blood and tumour and reduced immunosuppressive effect of MDSCs over CD3+CD4+T cell proliferation.<br>• Non-significant reduction in metastatic lung nodules. |
| Kim et al., 2020. Ref. (90) | • BALB/c mice<br>• 4T1 murine breast cancer cell line | Treadmill running, low (10 m/min) or moderate intensity (15 m/min on a | • Reduced breast tumour latency and growth in low-intensity group.<br>• No effect on cell proliferation. |

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| | implanted orthotopically. | slope of 2.5°), for 5 days/week, 13 weeks. Started before tumour inoculation and continued after it. Mice were fed a high fat diet. | • Increased apoptosis in tumours in low-intensity group.<br>• Decreased number of M2 macrophages in both exercising groups, no effect on M1 macrophages.<br>• Myostatin inhibited M2 polarization *in vitro.* |
| Gomes-santos et al., 2021. Ref. (70) | • C57BL/6 wild-type and Cxcr3−/−, FVB and Balb/c mice<br>• E0771, EMT6, MMTV-PyMT, MCa-M3C murine breast cancer cell lines, implanted orthotopically. | Treadmill running, progressing from 30 min to 45 min, daily, moderate-to-vigorous intensity, starting when tumours reached ~20 or 100 mm3, until end of experiment | • Reduced tumour growth and metastatic burden.<br>• Tumour vessels' maturation and decreased hypoxia.<br>• Increased CD8+ T cells in tumours, chemokines mediated.<br>• Gene expression: reduced glucose uptake/insulin pathways, upregulation of oxidative metabolism and cytokine activation and downregulation of pathways involved with. immunosuppression in breast cancer. |
| Kurz et al., 2022. Ref. (99) | • Pancreatic cancer genetic model<br>• p48Cre/+; LSL-KRasG12D/+ C57BL/6 mice p53R172H/+; KRASG12D/+; pdx-1Cre/+ (KPC) cells implanted orthotopically. | Treadmill running, low-intensity, 30 mins/day, 5 days/week. Starting 1 or 12 days after tumour inoculation | • Reduced tumour initiation and progression.<br>• Antitumoral effects of exercise dependent on: CD8+T cells and their IL-15/IL-15Rα axis, beta-adrenergic signalling, and lymphocyte egress of from blood and secondary lymphoid organs. |

[3] TCA: tricarboxylic acid. MDSCs: myeloid-derived suppressor cells. DCs: dendritic cells. Tregs: regulatory T cells. IFN γ: interferon gamma. TNF α: tumour necrosis factor alpha. IL 12: interleukin 12. IL-15: interleukin 15. IL-15Rα: Interleukin 15 receptor alpha.

**Table 4:** Overview of clinical studies reporting immunomodulatory effects of exercise in cancer patients

| Ref | Cancer type | N | Intervention | Outcomes |
|---|---|---|---|---|
| Zylstra et al., 2022. Ref. (188) | Oesophageal adenocarcino-ma | 40 | • AE+RT, moderate intensity, supervised, during NACT.<br>• Control arm: no restrictions on physical activity. | • Higher rates of tumour regression (Mandard scoring system).<br>• Higher circulating CD3+ and CD8+ lymphocytes. |
| Ligibel et al., 2019. Ref.(103) | Breast cancer | 49 | • 60-90 min supervised: 20 minutes of RT + 30-45 minutes of moderate-intensity AE/ session, 2 sessions/week, + up to 180 min of unsupervised, moderate-intensity, aerobic exercise. For 3-6 weeks, pre surgery.<br>• Control arm: book + relaxation audio guide | • Upregulation of pathways implicated in immunity and inflammation.<br>• Trend towards a decrease in T regs cells in tumours. |
| Kurz et al., 2022. Ref. (99) | Pancreatic ductal adenocarcino-ma | 70 | • 60 min AE + 60 min RT/ week, unsupervised, during NACT or chemoradiation.<br>• Controls: historical data. | • Increased infiltration of CD8+ T cells.<br>• Trend toward higher expression of granzyme B in tumours.<br>• Increase in the median overall survival of patients with high levels of CD8 or granzyme B. |
| Glass et al., 2015. Ref. (68) | Solid tumours | 44 | • 20-45 min AE, 3 sessions/ week, for 12 weeks, + cytotoxic therapy and synthetic erythropoietin.<br>• Control arm: usual care. | • Trend toward higher circulating CD8+T cells and CD8+CD45RA+ T cells.<br>• Decreased in pro-inflammatory cytokine and angiogenic factors. |
| Pal et al., 2021. Ref. (126) | Breast and prostate cancer | 21 | • 6–52 weeks after the end of primary therapy.<br>• Acute exercise with cycle ergometer (cardiopulmonary exercise tests).<br>• Chronic exercise with cycle ergometer (12 weeks):<br>-Standard endurance: 30 min at vigorous intensity, 2 sessions/week<br>-Polarized endurance: HIIT 4 times 4 min at 85–95% HR peak and 3 times 3 min recovery at 70% HR peak, 1 session/week + moderate-intensity continuous training at the first lactate threshold, 1 session/ week. | • Lower expression of inhibiting NK cell receptor KIR2DL1 after acute exercise.<br>• Increased expression of the activating NK cell receptor NKG2D in the polarized group compared to the endurance standard group after 12 weeks of intervention. |

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| Toffoli. et al., 2021. Ref. (161) | Colon and breast cancer | 14 | • 30 min AE + 20 min RT, 2 sessions/week, moderate-high intensity, supervised. During first 9– 12 weeks of (neo)adjuvant chemotherapy.<br>• Control arm: no exercise but offered the intervention during the second half of chemotherapy. | • Preserved NK cell degranulation after chemotherapy.<br>• Higher expression of the activating receptor NKp46 on CD56dimCD16+ NK cells.<br>• Trend towards increased cytotoxicity.<br>• Trend towards increased IL-6 levels. |
| Fairey et al., 2005. Ref. (54) | Breast cancer survivors | 53 | • 3 AE sessions/week. Progressive, 15 min for weeks 1–3 and then systematically increased by 5 min every 3 weeks to 35 min for weeks 13–15. Intensity 70–75% of peak oxygen consumption. Supervised.<br>• Control arm: no Exercise. | • Increased NK cells cytotoxic activity.<br>• Increased unstimulated peripheral lymphocytes proliferation. |
| Schauer et al., 2022. Ref. (141) | Prostate cancer | 20 | • One acute bout of AE in a cycle ergometer: watt-max test followed by four high-intensity intervals of 1 min, interspersed by 3 min of recovery at 30% of watt-max. Before radical prostatectomy.<br>• Pre versus post intervention. | • Increased blood concentration of monocytes, neutrophils, and lymphocytes.<br>• Preferential mobilization and egress of CD56dim over CD56bright NK cells, and CD8 T cells with more pronounced mature and cytotoxic phenotype, potentially accompanied by cell exhaustion (CD8+ CD57+ NKG2C+ Granzyme-B+ Perforin bright TIGIT+).<br>• Increased NK cytotoxic activity against prostate cancer cell lines K562 and LNCaP but not PC-3. Decreased NK cytotoxic activity per-cell during exercise but improved 1-h post-exercise against all three cell lines. |

AE: aerobic exercise. RT: resistance training. NACT: neoadjuvant chemotherapy. HIIT: high intensity interval training.

**Table 5:** Overview of preclinical and clinical studies using dietary restriction + exercise in cancer.

| Preclinical studies using caloric restriction and exercise in cancer models. | | | |
|---|---|---|---|
| **Ref** | **Model** | **Intervention** | **Outcomes** |
| Xie et al., 2007. Ref. (177) | SENCAR mice (enhanced susceptibility to TPA-promoted skin carcinogenesis) | Experimental groups<br>• AL sedentary (Control)<br>• AL + Exe<br>• Pair-fed + Exe (paired-fed at the same amount as the control group)<br>• 20% CR<br>• Exe + 20% CR<br>CR: 20% less total calories from carbohydrates and fat for 12 weeks<br>Exe: treadmill exercise 60 min/day, 5 day/week for 10 weeks. | • Reduced IGF-1 levels in CR and Exe + CR groups.<br>• CR abrogated both Ras and PI3K signalling.<br>• Increase in caspase-3-like proteolytic activity in Exe +CR compared to control. |
| Turbitt et al., 2019. Ref. (162) | BALB/c mice<br>4T1 murine breast cancer cell line implanted orthotopically. | Experimental groups<br>• AL, sedentary (Control)<br>• Exe<br>• 10% CR<br>• Exe + 10% CR.<br><br>CR: 20% less total calories<br>Exe: voluntary wheel running.<br>Starting 8 weeks before tumour inoculation and continued after. | Exe + CR:<br>• Delayed tumour growth, reduced metastatic burden, and improved survival.<br>• Increased CD8+T cells and decreased MDSCs infiltration.<br>• Reduced the expression level of metastatic and immunosuppressive genes. |

| Clinical studies using dietary restriction + exercise in cancer patients. | | | | |
|---|---|---|---|---|
| **Ref** | **Cancer type** | **N** | **Intervention** | **Outcomes** |
| Albrecht et al.,2012. Ref. (3) | Advanced ovarian cancer | 1 | • Fasting of 18 h + 3.33 g flaxseed oil/kg body weight + two 200 mg dose of caffeine+ at least 90 minutes of exercise in treadmill. During 3 consecutive days for 3 consecutive months. | • CA-125 levels increased, but no signs of disease progression on CT scan.<br>• Positive lifestyle modifications.<br>• Improvements in anxiety, perceived stress, emotional functioning, and physical symptoms of peripheral neuropathy. |

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|---|---|---|---|---|
| Harvie et al., 2021. Ref. (77) | Breast cancer | 172 | • Intermittent fasting group (IER): before CT, 2 days of 650-1000 kcal, 50 g carbohydrate, 50–70 g protein, 30–40 g fat).<br>• Continued caloric restriction group (CER): Mediterranean diet, 30% energy from fat, 25% energy from protein and 45% from low glycaemic load carbohydrates, 5 portions of vegetables and 2 portions of fruit per day, alcohol to <10 U/week). Tailored to their energy requirements for weight loss (up to 25% energy restriction) or maintenance, depending on baseline BMI.<br>• PA recommendation: 5 × 30 minutes of moderate intensity physical activity/ week & 2–3 sessions resistance exercise/week During adjuvant or neoadjuvant chemotherapy. | • Feasible.<br>• Reported baseline PA was maintained at 3 weeks post chemotherapy in both groups. |
| Orgel et al., 2021. Ref. (125) | Acute lymphoblastic leukemia (10 to 21 years of age) | 40 | Caloric deficit of ≥10% and a home-based exercise intervention combining aerobic +resistance training, 15- to 30-min/day, daily (200 min/week). During the 4 weeks of induction chemotherapy. | • Feasible.<br>• Reduced minimal residual burden risk.<br>• Decreased fat gain in overweight and obese patients. |

AL: ad libitum. Exe: exercise CR: caloric restriction. MDSCs: myeloid-derived suppressor cells.

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