Impact of physical activity and energy restriction on immune regulation of cancer

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Abstract: Cancer is a major public health issue worldwide. Lifestyle factors, such as body weight and physical activity (PA), significantly impact cancer risk and progression. There is strong evidence that PA reduces and obesity increases risk and mortality from numerous cancer types. Energy restriction (ER) in non-obese hosts significantly reduces tumor incidence in a variety of preclinical models, and reduces body weight and cardiometabolic risk factors in humans. Emerging data suggest that PA- and ER-induced changes in inflammatory and immune mediators may contribute to the cancer prevention effects of these interventions. A systematic literature search was conducted to identify studies that evaluated the impact of PA and ER on tumor and immune outcomes in humans and animal models. A total of 97 eligible studies were identified (68 studies reporting PA interventions and 30 studies reporting ER interventions). Thirty-one studies investigated the effect of PA on cancer immune outcomes using preclinical cancer models of breast (n=17, 55%), gastrointestinal (n=6, 19%), melanoma (n=4, 13%), and several other cancer types (n=4, 13%). Despite the heterogeneity in study designs, the majority of studies (n=23, 74%) reported positive effects of PA on tumor outcomes. Thirty-seven clinical studies investigated the effect of PA on cancer immune outcomes. None reported tumor outcomes, thus only immune outcomes were evaluated in these studies. PA studies were conducted in patients with breast (n=22, 59%), gastrointestinal (n=5, 14%), prostate (n=2, 5%), esophageal (n=1, 3%), lung (n=1, 3%) cancer, leukemia (n=1, 3%), or mixed cancer types (n=5, 14%). Twenty-two studies investigated the effect of ER interventions on cancer immune outcomes using preclinical cancer models including breast (n=5, 23%), gastrointestinal (n=5, 23%), lung (n=2, 9%), liver (n=2, 9%), pancreatic (n=2, 9%), and several other cancer types (n=6, 27%). Positive effects of ER on tumor outcomes were reported in 21 of 22 studies. Six clinical studies investigated the effect of ER (in combination with PA) on tumor immune outcomes in cancer patients with overweight or obesity. Five were conducted in breast cancer patients, and one recruited patients of a mix of cancer types. A wide range of immunological parameters including immune cell phenotype and function, cytokines, and other immune and inflammatory markers were assessed in multiple tissue compartments (blood, spleen, lymph nodes and tumor) in the included studies. Results from preclinical and clinical studies suggest that both PA and ER exert heterogeneous effects on circulating factors and systemic immune responses. PA + ER alters the gene expression profile and immune infiltrates in the tumor which may result in a reduction in immune suppressive factors. However, additional studies are needed to better understand the effect of PA and/or ER on immunomodulation, particularly in the tumor microenvironment (TME).

Introduction

Cancer is a major public health problem with an estimated 17 million new cases and 9.5 million cancer deaths in 2018 worldwide (1). Like many chronic diseases, the incidence and prevalence of cancer increase with age (2). Lifestyle factors, such as body weight and physical activity (PA), significantly impact cancer risk and progression. There is strong evidence that PA is associated with reduced risk of breast, colorectal, and endometrial cancer (3,4). Suggestive evidence also exists for the association between PA and reduced risk of cancer in the esophagus, lung and liver (3,4). In addition, PA is associated with decreased cancer recurrence, cancer-specific and all-cause mortality in patients with breast, colorectal and prostate cancer (5-7).

Numerous epidemiological studies demonstrate that overweight and obesity are a strong risk factor for multiple cancer types. The International Agency for Research on Cancer (IARC) working group reported that there is sufficient evidence to conclude that excess body fatness (overweight and obesity) is associated with increased risk of 13 types of cancers including esophagus, gastric, colorectum, liver, gallbladder, pancreas, postmenopausal breast, uterine, ovary, kidney, meningioma, thyroid, and multiple myeloma (8). Although the association between obesity and cancer survival is debated (9), obesity is associated with lower survival in patients with ovarian (10), endometrial (11), and breast cancer (12,13).

Evidence is emerging that weight loss may reduce obesity-associated cancer risk (14). Multiple studies demonstrate a reduction in cancer risk in bariatric surgery patients (15-19) that is attributed specifically to weight loss (20). Among the obesity-associated cancers, bariatric surgery is associated with lower risk of postmenopausal breast, endometrial and colon cancer (21-23). Results from the large Cancer Prevention Study II Nutrition Cohort Study in postmenopausal women suggest that a sustained loss of 10% of body weight may be associated with a modest reduction in risk for breast cancer (24). However, the minimum amount of weight loss required to reduce obesity-associated cancer risk may differ by cancer site and the type of weight loss intervention utilized. Thus, additional studies are needed to address this question.

ER in non-obese hosts has been studied extensively in animal models and is the only known intervention to prolong lifespan in numerous species, including non-human primates (25,26). Furthermore, ER in non-obese hosts can reduce tumor incidence and progression in a variety of preclinical tumor models (27,28). In humans, two years of total energy or calorie restriction was evaluated in the CALERIE-2 (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) trial to assess the effect of ER on biomarkers of longevity and cardiometabolic risk among non-obese adults (29). The calorie-restricted group achieved 11.9%±0.7% ER over two years and had lower body weight, waist circumference and fat mass compared to the control group at 24 months (30). Furthermore, ER in non-obese adults reduces cardiometabolic risk factors, including LDL-cholesterol, total cholesterol to HDL-cholesterol ratio, systolic and diastolic blood pressure and the inflammatory mediator, C-reactive protein (CRP) (31). However, no data on cancer outcomes has been reported from this trial.

Despite compelling observational and experimental data supporting the association between changes in host energy balance and cancer outcomes, the underlying mechanisms are not completely understood. Previous studies suggest that changes in metabolic, endocrine, inflammatory and immune mediators may contribute to the cancer prevention effect of PA and ER (32-34). The metabolic and endocrine pathways altered by PA and ER are reviewed elsewhere (34-36). Emerging data suggest that PA- and ER-induced changes in inflammatory and immune mediators may also be important mediators underlying the cancer prevention effects of these interventions, and is the focus of this review.

The fundamental role of the immune system in tumor development has long been recognized and involves a complex network of pro- and anti-tumor mediators. CD8+ cytotoxic T cells (CTLs) and natural killer (NK) cells are primarily responsible for the killing of tumor cells, while CD4+ helper T cells can enhance their cytotoxic function by producing cytokines such as IFNγ (37,38). However, immunosuppressive cells from both the myeloid [myeloid-

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derived suppressor cells (MDSCs)] and the lymphoid [regulatory T cells (Tregs), a subset of T cells with immune suppressive capacity] lineages are also recruited in response to tumor-derived signals to facilitate immune escape (37,38). In addition, a wide variety of cytokines and chemokines also play important roles in dictating the immune and inflammatory milieu and the function of immune cells (37,38).

In healthy humans or rodent models, regular, moderate intensity PA enhances neutrophil, NK cell and T cell function, enhances vaccine responses, reduces T cell exhaustion, and alters inflammatory responses (39-42). PA also ameliorates and delays immunosenescence, the deterioration of the immune system with advanced age, which is postulated to contribute to an increase in cancer risk (2,43). Less is known about the effects of PA on immune function in tumor-bearing hosts. Emerging evidence suggest that PA may result in an increase in effector cell number and function, a reduction in immunosuppressive cells, and an altered cytokine profile in tumor-bearing animals (32,44,45). However, a definitive link between PA and improved cancer immunity is yet to be established.

The beneficial effects of ER on immune function include a reduction in chronic inflammation and a delay in immunosenescence. Animal studies suggest that ER reduces pro-inflammatory cytokines produced by mononuclear cells, as well as in the circulation (27,28,46). In addition, ER maintains naïve T cell numbers and T cell proliferation capacity in both aged rodents and non-human primates (27,47). How ER may be modulating host immunity in tumor-bearing hosts is not well understood. Studies in preclinical cancer models demonstrate that ER may result in a reduction in tumor-infiltrating macrophages, MDSCs, and circulating and intratumoral pro-inflammatory mediators (34,45).

Several reviews have summarized the effect of PA on tumor outcomes, or the potential mechanisms underlying the effect of PA on immune function at various stages of cancer development (32,33,48-51). The cancer prevention effect and potential changes in cancer immunity induced by ER have also been discussed briefly in several reviews (27,28,34,52). However, no studies have assessed the evidence linking potential immune mechanisms to the beneficial effect of PA and ER across the cancer continuum. Therefore, the objective of the current review was to evaluate and summarize the findings from both preclinical and clinical studies that have examined the effect of PA and/ or ER on immune outcomes in tumor-bearing hosts.

Methods

Search strategy

A systematic literature search was conducted using PubMed (Medline), Web of Science and CENTRAL to identify studies that evaluate the impact of PA and ER on tumor and immune outcomes in animal models and in humans. The search strategy included three sets of search terms: (I) PA, ER, and related terms; (II) immunological parameters including cellular and molecular mediators of immunity and inflammation, key immunological events and immunotherapy; (III) cancer of all types (complete search strategy provided in *Table S1*). Supplemental searching by hand was also conducted to identify additional studies from the reference lists of relevant review and primary research articles.

Inclusion and exclusion criteria

Only primary research articles written in the English language were included. Intervention studies conducted in preclinical cancer models or human cancer patients were included, while observational studies or intervention studies conducted in non-cancer subjects were excluded. Eligible preclinical studies must have reported the effect of energy balance interventions on tumor outcomes (tumor incidence, growth, metastasis or survival). Few clinical studies investigated the effect of energy balance interventions on tumor outcomes; therefore, this criterion was not applied to clinical studies. We focused on studies that evaluated the effect of chronic, aerobic activity (such as running and swimming) as the intervention. Studies performing resistance exercise, conditioning or stretching exercise (e.g., Tai Chi or yoga), or a single bout of exercise were excluded. Numerous studies combined resistance exercise with aerobic exercise interventions to prevent muscle wasting and cachexia in cancer patients. Therefore, we included clinical studies that applied a combination of aerobic and resistance exercise, and excluded studies that solely used resistance exercise training. Because weight loss and wasting are common phenomena in late-stage cancer patients experiencing cancer cachexia, we excluded studies that reported weight loss as a secondary outcome to cancer progression, and only included studies performing intentional weight loss intervention via PA and/or ER. Included studies must have assessed immune outcomes, including immune cell number and/or function, gene expression or protein level of immune and inflammatory

markers. Studies that included multiple interventions (such as those investigating the effect of PA and chemotherapy as single intervention or in combination) were included, as long as it was possible to compare between no intervention and energy balance intervention alone groups.

Study selection, data extraction and analysis

EndNote software was used to manage records from the literature search. After de-duplication, the titles and abstracts of all obtained records were first reviewed to determine whether each record met the inclusion criteria. Potentially eligible studies were further reviewed on the full texts to determine the eligibility based on the inclusion and exclusion criteria. Findings were summarized separately on the effect of PA and ER, with each category further divided into preclinical and clinical findings.

Results

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (53) flow diagram is shown in *Figure S1*. A total of 97 eligible studies were identified, including 68 studies (31 preclinical and 37 clinical studies) reporting PA interventions, and 30 studies (24 preclinical and six clinical studies) reporting ER interventions. One preclinical study (45) investigated the effects of PA and ER separately and in combination, and was included in the summary of both PA and ER studies.

Effects of PA on cancer immune outcomes

Preclinical findings

Thirty-one studies investigated the effect of PA interventions on cancer immune outcomes using preclinical (mouse or rat) cancer models (*Table 1*). Breast cancer was the most studied cancer type (n=17, 55%) (45,54-69), followed by gastrointestinal cancer (n=6, 19%) (70-75), melanoma (n=4, 13%) (44,76-78) and several other cancer types (n=4, 13%) (79-82). Transplantable, carcinogen-induced and genetically-engineered (spontaneous) cancer models were used. Among the transplantable tumor models, subcutaneous (s.c.) inoculation was the most common route of tumor inoculation. Orthotopic (intramammary) inoculation was applied in four studies using breast cancer models (45,57,58,61) to mimic the natural tissue environment of mammary tumorigenesis. Several studies inoculated tumor cells via intravenous (i.v.) (62,78-80)

or intraperitoneal (i.p.) routes (81) where no primary tumors were formed, thus lung metastasis and peritoneal fluid were assessed as tumor outcomes, respectively. All studies reporting intestinal cancer outcomes (70-75) used carcinogen-induced or genetically-engineered cancer models, and intestinal lesions (aberrant crypt foci or polyps) were assessed as indicators of tumorigenesis.

PA modalities included voluntary wheel running, treadmill running and swimming. The frequency, intensity, duration of individual PA sessions, and the length of total PA intervention period were highly heterogeneous. Furthermore, the window of PA intervention in relation to the cancer continuum was also variable. Despite the heterogeneity in study designs, the majority of studies (n=23, 74%) reported positive effects of PA on tumor outcomes including reduced tumor incidence, tumor growth, metastases, and improved survival. Six studies (19%) (62,64,69,76,78,79) reported null effects, and two studies (6%) (66,80) reported negative effects of PA on tumor outcomes.

Commonly reported immune outcomes included immune cell phenotype and function, cytokines and other immune and inflammatory markers. Tumor, spleen and blood were the most frequently assessed tissue compartments. In the spleen, the percentage and/or number of NK cells was increased in two studies (77,80) and unchanged in one study (79), while NK cell cytotoxicity was increased in three studies (62,79,80) and unchanged in one study (44). One study reported no change in the number of splenic T cells (77), and two studies reported mixed findings on T cell functional markers (57,77). Increased CD4$^+$ T cell proliferation (by PA+ER) (45) and macrophage phagocytic activity (81) were each reported in one study. Circulating immune cell populations were assessed in three studies, with two null findings (66,75) and one reporting an increase in total leukocytes, neutrophils, and monocytes (61). Among the serum inflammatory markers evaluated, TNFα was reduced in three studies (68,70,72) and increased in one study (55), IL-6 was reduced in three studies (65,72,74) and unchanged in one study (59), MCP-1 was reduced in one study (65) and unchanged in two studies (58,78), and CRP was unchanged in two studies (59,68). A few studies also assessed immune outcomes in other tissue compartments. One study reported an increase in the percentage of CD8$^+$/IFNγ$^+$ cells in the tumor-draining lymph node (TDLN) (77), and three other studies reported an increase in lymphocyte proliferation from the non-TDLN (55,56,76).

Among the tumor immune infiltrates, the percentage

Table 1 Preclinical findings on the effects of PA on cancer immune outcomes

Reference	Tumor model	PA modality	PA protocol	PA/tumor timeline	Tumor outcomes	Immune outcomes	
						PA effect	PA no effect
(I) Breast cancer, transplantable model (n=12)							
Hagar et al., 2019	Female Balb/c mice, 4T1 mammary tumor (orthotopic inoculation)	Motorized wheel running	10–26 min/day, 5 days/wk, 8 wks	Tumor inoculation 72h after the completion of PA intervention and lasted 8 wks	↓Mean tumor size and tumor doubling time; ↑survival	↑Circulating leukocytes, neutrophils, monocytes; ↓Intratumoral Tregs, CD8+/FoxP3+ ratio	Intratumoral CD8+ T cells
Molanouri et al., 2019	Female Balb/c mice, 4T1 mammary tumor (s.c. inoculation)	Treadmill running	50 min/day at 50–70% VO$_2$max, 5 days/wk, 12 wks	PA from 6 wks before to 6 wks after tumor inoculation	No change in tumor volume	↓IL-4 within the tumor; ↓IL-4, ↑IFNγ, ↑IFNγ/IL-4 ratio produced by stimulated splenocytes	TNFα, IL-6, IFNγ within the tumor
Bianco et al., 2017	Female Balb/c mice, 4T1 mammary tumor (orthotopic inoculation)	Swimming	15–45 min/day, 5 days/wk, 4 wks	PA initiated at tumor inoculation and lasted 4 wks	↓Tumor volume	↑Th1 markers, ↓Th2 markers, ↓%Treg cells in the spleen; ↓%TIDCs, ↑CD80+/CD86+ TIDCs; ↑%BMDCs, CD80+/CD86+ BMDCs, ↓IL-10 production by BMDCs	%Tumor-infiltrating CD4+ and CD8+ T cells, macrophages
Turbitt et al., 2019	Female BALB/c mice, 4T1.2 mammary tumor (orthotopic inoculation)	Voluntary wheel running (alone or in combination with 10% ER)	Access to running wheels, 13 wks	PA from 8 wks before to 5 wks after tumor inoculation	↓Tumor growth; ↓lung and femur metastasis; ↑survival (all effects by PA + ER)	↓MDSC accumulation, ↑CD4+ T cell proliferation in the spleen (PA+ER); ↓tumor-infiltrating MDSCs, ↑CD8+ T cells, CD8+:MDSC ratio (PA+ER); altered inflammatory and immune pathways within the tumor	–
Buss and Dachs, 2018	Female C57BL/6 ApoE−/− mice, EO771 mammary tumor (orthotopic inoculation)	Voluntary wheel running	Access to running wheels, 16 days	PA initiated at tumor inoculation and lasted an average of 16 days	↓Incidence of abdominal metastasis; no change in tumor growth rate	–	Number of tumor-infiltrating T cells, %CTLs or %Tregs of total T cells; serum MCP-1
Shalamzari et al., 2014	Female BALB/c mice, MC4-L2 mammary tumor (s.c. inoculation)	Treadmill running	25–40 min/day, 5–7 days/wk, up to 14 wks	PA from 8 wks before to 6 wks after tumor inoculation	↓Tumor growth	↓IL-6 within the tumor	–

Table 1 (*continued*)

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Reference	Tumor model	PA modality	PA protocol	PA/tumor timeline	Tumor outcomes	Immune outcomes PA effect	Immune outcomes PA no effect
Khori et al., 2015	Female BALB/ c mice, MC4-L2 mammary tumor (s.c. inoculation)	Treadmill running	10–14 min/day, 5 days/wk, 5 wks	PA initiated at tumor inoculation and lasted 5 wks	↓Tumor size	↓IL-6 within the tumor	–
Woods et al., 1994	C3H/HeN mice, SCA-1 mammary tumor (s.c. inoculation)	Treadmill running (moderate vs. exhaustive)	30 min or until exhaustion/day, 17 days	PA from 3 days before to 14 days after tumor inoculation	No change in tumor incidence or progression	↑Tumor-infiltrating macrophage phagocytic activity (moderate EX)	–
Hoffman-Goetz et al., 1994	Female BALB/ c mice, MMT 66 mammary tumor (i.v. inoculation)	Treadmill vs. voluntary wheel running	30 min/day (treadmill) or access to running wheels, up to 11 wks	PA from 8 wks before to 3 wks after tumor inoculation	No change in lung metastasis	↑Splenic NKCC, LAK activity	–
Almeida et al., 2009	Male Swiss mice, Ehrlich mammary tumor (s.c. inoculation)	Swimming	1 h/day at 50% of maximal capacity, 5 days/ wk, 6 wks	PA from 4 wks before to 2 wks after tumor inoculation	↓Tumor volume and weight	↓Macrophage and neutrophil infiltration in the tumor	–
Bacurau et al., 2007	Male Wistar rats, Walker 256 mammary tumor (s.c. inoculation)	Treadmill running	30 min/day at 85% VO_2max, 5 days/wk, 10 wks	PA from 8 wks before to 15 days after tumor inoculation	↓Tumor mass / body weight ratio; ↑survival	↑Plasma IL-1, TNFα;↑mesenteric LN lymphocyte proliferation	Plasma IL-2; peritoneal macrophage phagocytosis
Bacurau et al., 2000	Male Wistar rats, Walker 256 mammary tumor (s.c. inoculation)	Treadmill running	1 h/day at 60% VO_2max, 5 days/ wk, 10 wks	PA from 8 wks before to 14 days after tumor inoculation	↑Survival	↑Mesenteric LN lymphocyte proliferation; ↑peritoneal macrophage phagocytosis	–
(II) Breast cancer, carcinogen-induced model (n=3)							
Faustino-Rocha et al., 2017	Female Sprague-Dawley rats, MNU-induced mammary tumor	Treadmill running	60 min/day, 5 days/wk, 35 wks	PA initiated after tumor induction and lasted 35 wks	↓Tumor number; no change in tumor weight	–	Serum IL-6, CRP
Thompson et al., 2010	Female Sprague-Dawley rats, MNU-induced mammary tumor	Motorized vs. voluntary wheel running	Access to motorized or nonmotorized wheels	PA initiated 1 wk after tumor induction	↓Tumor incidence and multiplicity	↓Plasma IL-1α, IL-1β, TNFα; ↑Plasma IL-2, GM-CSF, IFNγ, IL-4, IL-6, IL-10	Plasma CRP

Table 1 (*continued*)

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Table 1 (*continued*)

Reference	Tumor model	PA modality	PA protocol	PA/tumor timeline	Tumor outcomes	Immune outcomes	
						PA effect	PA no effect
Saez et al., 2007	Female Sprague–Dawley rats, DMBA-induced mammary tumor	Swimming	30 min/day, 5 days/wk, 1–2 months	PA initiated after the appearance of the 1st tumor and lasted 1–2 months	↑Tumor growth; no change in tumor multiplicity	–	%Circulating NK cells
(III) Breast cancer, genetically-engineered (spontaneous) model (n=2)							
Murphy et al., 2011	Female C3(1) SV40Tag mice, spontaneous mammary tumor	Treadmill running	60 min/day at 70% VO₂max, 6 days/wk, 20 wks	PA initiated at 4 wks of age and lasted 20 wks	↓Spontaneous tumor number; ↓tumor volume	↓Plasma MCP-1 and IL-6	–
Goh et al., 2013	Female PyMT transgenic mice, spontaneous mammary tumor	Voluntary wheel running	Access to running wheels, 10 wks	PA initiated at 42 days of age and lasted 10 wks	↓Tumor growth	↓CCL22, ↑CXCR4 gene expression within the tumor	Spleen weight
(IV) Gastrointestinal cancer (n=6)							
Gazizadeh Darband et al., 2019	Male Wistar rats, DMH-induced colorectal cancer	Treadmill running	10–60 min/day, 5 days/wk, 8 wks	PA initiated after the completion of tumor induction and lasted 8 wks	↓Number of aberrant crypt foci	↓Serum TNFα, IL-6	–
Aoi et al., 2010	BALB/c mice, AOM-induced colon cancer	Treadmill running	15–30 min/day, 3 days/wk, 6 wks	PA initiated after the beginning of tumor induction and lasted 6 wks	↓Number of aberrant crypt foci and aberrant crypts	↓Colon TNFα gene expression; ↓Plasma TNFα	–
Frajacomo et al., 2015	Male BALB/c and C57BL/6 mice, MNNG-induced colon cancer	Swimming	20–60 min/day, 5 days/wk, 8 wks	PA initiated 14 days after the beginning of tumor induction and lasted 8 wks	↓Number of colon dysplastic lesions	↑IL-10 in the colon	IFNγ, IL-12, TNFα in the colon
McClellan et al., 2014	Male Apc^Min/+ mice, spontaneous intestinal tumor	Treadmill running	1 h/day, 6 days/wk, 12 wks	PA initiated at 4 wks of age and lasted 12 wks	↓Number of large polyps; no change in total polyp number	↓Intestinal gene expression of total, M1 and M2 macrophage markers; ↑CTL marker (CD8), ↓Treg marker (FoxP3)	Intestinal gene expression of M1 (IL-23, Nos2) and M2 (IL-4, IL-10) macrophage markers, MCP-1

Table 1 (*continued*)

Table 1 (*continued*)

Reference	Tumor model	PA modality	PA protocol	PA/tumor timeline	Tumor outcomes	Immune outcomes	
						PA effect	PA no effect
Zielinski et al., 2012	Male APC Min$^{+/-}$ mice, spontaneous intestinal tumor	Treadmill running	60 min/day, 6 days/wk, 11 wks	PA initiated at 4 wks of age and lasted 11 wks	↓Intestinal polyp number and polyp burden	↓IL-1, IL-6, TNFα production by LPS-stimulated peritoneal exudate cells	Circulating leukocytes, lymphocytes, monocytes, granulocytes
Mehl et al., 2005	Male and female Apc$^{Min/+}$ mice, spontaneous intestinal tumor	Treadmill vs. voluntary wheel running	60 min/day, 6 days/wk (treadmill) or access to running wheels, 9 wks	PA initiated at 4 wks of age and lasted 9 wks	↓Intestinal polyp number and size (treadmill, male only)	↓Plasma IL-6; ↓spleen weight (male only)	–
(V) Melanoma (n=4)							
Yan and Demars, 2011	Male C57BL/6 mice, B16BL/6 melanoma (i.v.) or Lewis lung carcinoma (s.c. inoculation)	Voluntary wheel running	Access to running wheels, 11–13 wks	PA from 9 wks before to 2–4 wks after tumor inoculation	No change in tumor volume or lung metastasis	–	Plasma MCP-1
Dos Santos et al., 2019	Female C57BL/6 mice, B16F10 melanoma (s.c. inoculation)	Treadmill running	1h/day at 45–55% maximum speed, 5 days/wk, 11–12 wks	PA from 8 wks before to 21–31 days after tumor inoculation	No change in tumor growth	↑Non-TDLN lymphocyte proliferation	%Th17 cells or Tregs of CD4$^+$ cells in non-TDLNs; Cytokine production by mitogen-stimulated lymphocytes from non-TDLNs
Pedersen et al., 2016	Female C57BL/6 mice, B16F10 melanoma (s.c. or i.v. inoculation)	Voluntary wheel running	Access to running wheels, 6–7 wks	PA from 4 wks before to 2–3 wks after tumor inoculation	↓Tumor volume; ↓lung metastasis	↑Tumor-infiltrating NK cells, CD3$^+$ T cells, DCs; ↑tumor gene expression of pro- and anti-inflammatory cytokines, markers of NK cells and NK cell activation and chemotaxis	Tumor-infiltrating CD4$^+$ or CD8$^+$ T cells, B cells, MDSCs; splenic NKCC

Table 1 (*continued*)

Table 1 (*continued*)

Reference	Tumor model	PA modality	PA protocol	PA/tumor timeline	Tumor outcomes	Immune outcomes	
						PA effect	PA no effect
Lee et al., 2019	C57BL/6 mice, B16F10 melanoma (s.c. inoculation)	Swimming at thermoneutral (TT) vs. body temperature (BT)	30 min/day, 6 days/wk, 3 wks	PA initiated 3 days after tumor inoculation and lasted 3 wks	↓Tumor growth (TT)	↑Splenic NK, NKT, CD8⁺ effector memory cells; ↑CD8⁺/IFNγ⁺ cells in the spleen and TDLN (all effects by TT)	Splenic CD4⁺, CD8⁺, γσT cells; Splenic CD4⁺/IFNγ⁺, CD4⁺/IL-4⁺, CD4⁺/IL-17⁺ cells
(VI) Other cancers (n=4)							
Macneil and Hoffman-Goetz, 1993	Male C3H mice, CIRAS1 tumor (i.v. inoculation)	Treadmill vs. voluntary wheel running	30 min/ day, 5 days/ wk (treadmill) or access to running wheels, 9 wks	Tumor inoculation at the completion of PA (9 wks) and sacrifice after 3 wks	↑Tumor multiplicity; no change in tumor incidence	↑Splenic NKCC (wheel); ↑%Splenic NK cells (treadmill)	–
Hoffman-Goetz et al., 1992	Male C3H mice, CIRAS3 tumor (i.v. inoculation)	Treadmill running	30 min/day, 5 days/wk, 8 wks	PA from 4 wks before to 4 wks after tumor inoculation	No change in lung metastasis	↑Splenic NKCC	%Splenic NK cells
Singh et al., 2005	Male BALB/c mice, Dalton's lymphoma (i.p. inoculation)	Treadmill running	90 or 120 min/ day, 10 days	PA initiated at tumor inoculation and lasted 10 days	↓Tumor progression (weight gain due to ascites)	↑Splenic macrophage cytotoxicity, production of IL-1, TNFα, NO	–
Zielinski et al., 2004	Female BALB/ c mice, EL-4 lymphoma (s.c. inoculation)	Treadmill running	3 h or until fatigue/day, up to 14 days	Tumor inoculation immediately after the 1st EX bout and lasted up to 14 days	Delayed tumor growth and faster tumor regression	↓Density of macrophages and neutrophils, ↑lymphocytes in the tumor	–

↑, increase (compared to control group); ↓, decrease (compared to control group). IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; MCP, monocyte chemoattractant protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; CCL, CC chemokine ligand; CXCR, CXC chemokine receptor; DC, dendritic cell; BMDC, bone marrow-derived DC; TIDC, tumor-infiltrating DC; NK, natural killer; NKCC, NK cell cytotoxicity; LAK, lymphokine activated killer; CTL, cytotoxic T lymphocyte; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; LN, lymph node; TDLN, tumor-draining lymph node; NO, nitric oxide; VO₂max, maximum oxygen consumption rate; DMBA, 7,12-dimethylbenz(a)anthracene; MNU, N-methyl-N-nitrosurea; AOM, azoxymethan; MNNG, N-methyl-N'-nitro-N-nitrosoguanidine; DMH, 1,2-Dimethylhydrazine; s.c., subcutaneous; i.v. intravenous; i.p., intraperitoneal; EX, exercise.

and/or number of T cells was increased in three studies (44,45,73) and unchanged in three studies (57,58,61). The percentage of NK cells was increased in one study (44), Tregs was reduced in two studies (61,73) and unchanged in one study (58). The percentage of MDSCs was reduced in one study by the combination of PA+ER (45). The percentage and/or number of macrophages was reduced in three studies (54,73,82) and unchanged in one study (57); and the phagocytic activity of tumor-infiltrating macrophages was increased in one study (69). The percentage of dendritic cells (DCs) was increased (44) or reduced (57), respectively, in one study, and the percentage of neutrophils was reduced in two studies (54,82). In addition to the infiltrating immune cells, several studies reported mixed findings on immune and inflammatory markers within the tumor. TNFα was increased in one study (44), reduced in one study (70), and unchanged in two studies (64,71). IL-6 was increased in one study (44), reduced in two studies (63,67), and unchanged in one study (64). IFNγ was increased in one study (44), reduced in one study (45), and unchanged in two studies (64,71). Two studies assessed the gene expression profile within the tumor microenvironment (TME) in a melanoma (44) or breast cancer (45) model, respectively, and both found global changes in an array of immune and inflammatory mediators including cytokines, chemokines and receptors, and multiple immune inhibitory molecules.

Clinical findings

Thirty-seven clinical studies investigated the effect of PA interventions on cancer immune outcomes (*Table 2*). The majority of studies were conducted in patients with breast cancer (n=22, 59%) (83-104). Other studies involved patients with gastrointestinal cancer (n=5, 14%) (105-109), prostate cancer (n=2, 5%) (110,111), esophageal cancer (n=1, 3%) (112), lung cancer (n=1, 3%) (113), leukemia (n=1, 3%) (114) or mixed cancer types (n=5, 14%) (115-119). Twenty-two studies used solely aerobic exercise interventions and fifteen studies used a combination of aerobic and resistance exercise interventions. Treadmill and cycle ergometer were most frequently used in the aerobic exercise sessions. Similar to preclinical PA studies, much heterogeneity existed in all aspects of PA prescription (frequency, duration, intensity, and length of intervention period). Several clinical studies used a single-group design where all participants performed the PA intervention. As a result, no comparison can be made between the PA intervention and sedentary control. Instead, immune

outcomes pre- and post-PA intervention were compared.

The timing of the PA intervention in relation to cancer treatment may significantly affect cancer immune outcomes. Therefore, we classified the included studies into three categories: PA interventions given before, during, and after treatment. The existing evidence base only includes two pre-treatment (pre-surgical) (94,113) and eight during-treatment (93,95,101,110,114,115,117,119) PA studies, while the majority of studies (n=27) assessed the effect of PA interventions post-cancer treatment.

Most included studies assessed the effect of PA intervention on serum immune and inflammatory cytokines, the majority of which reported null results (83,85,87-92,94,99,100,102,103,105,108,110,115-117,119). Several studies also compared post-PA intervention to pre-PA intervention serum cytokine levels, with mixed results showing either a reduction (84,104,107,112,114) or no change in serum cytokines after the PA intervention (84,104,106,107,111-114,118).

Circulating immune cell phenotype and function were also commonly evaluated. When comparing the PA intervention group to the sedentary control, the percentage and/or number of T cells was increased in one study (116) and unchanged in four studies (90,96,101,115), while no change was found by any study in circulating B cells, NK cells, monocytes or neutrophils. Regarding immune cell function, NK cell cytotoxicity was increased in two studies (86,109) and unchanged in two studies (96,115), lymphocyte proliferation was increased in two studies (86,90), and lymphocyte cytokine production was reported in four studies with mostly no change (83,86,90,105). When comparing post-PA intervention to pre-intervention, one study reported a reduction in the percentage of lymphocytes and monocytes and an increase in granulocytes (98), while two other studies reported no change in the percentage of T cells or NK cells (93,97). One study reported increased NK cell cytotoxicity post PA intervention (97).

Due to limited access to tumor tissue biopsies, most clinical studies evaluated immune outcomes only in the blood, with only one exception where tumor samples were analyzed after a pre-surgical PA intervention (94). In this study, a pre-surgical exercise intervention lasting approximately a month resulted in global changes in the gene expression profile within the TME, with an upregulation of pathways involved in immune cell function and inflammatory signaling reported in the exercise compared to the sedentary control group. A trend toward a decrease in the percentage of tumor-infiltrating Tregs

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Table 2 Clinical findings on the effects of PA on cancer immune outcomes

Reference	Participants	PA/tumor timeline	Intervention groups	PA modality	PA protocol	Immune outcomes	
						PA effect	PA no effect
(I) Before treatment (n=2)							
Ligibel et al., 2019	Newly diagnosed breast cancer patients	Between enrollment and surgery	Intervention (n=27); control (n=22)	Aerobic + resistance exercise	180 min aerobic + 40 min strength training/wk, for a mean of 29.3 days	↑Inflammatory and immune pathways within the tumor; ↓tumor-infiltrating Tregs	Serum CRP, IL-6; tumor-infiltrating CD4+, CD8+, CD56+, CD163+ cells
Jones et al., 2009	Non-small cell lung cancer patients	Between enrollment and surgical resection	Pre-post intervention (n=12)	Aerobic exercise (cycling)	20–30 min/session, at 60–65% VO2peak, 5 sessions/wk until surgical resection	↓Serum ICAM-1	Serum CRP, MIP-1α, IL-6, IL-8, MCP-1, TNFα
(II) During treatment (n=8)							
Mijwel et al., 2019	Breast cancer patients	During adjuvant chemotherapy	Intervention (n=72); control (n=60)	Aerobic exercise (cycling)	20 min aerobic exercise (at RPE 13–15) + 10 min HIIT (at RPE 16–18)/session, 2 sessions/wk, 16 wks	–	Circulating lymphocyte and neutrophil concentration
Schmidt et al., 2018	Breast cancer patients	During adjuvant chemotherapy	Intervention (n=21); control (n=26)	Aerobic exercise (cycling)	45 min/session at Borg level of 11–14, 2 sessions/wk, 12 wks	–	Circulating CD3, CD4, CD8, αβ, γσ T cells, CD19 B cells, CD16/CD56 NK cells
Kim et al., 2015	Breast cancer patients	During chemotherapy	Pre-post intervention (n=20)	Aerobic exercise (walking)	40–60 min/session at 40–60% HRR, 5 sessions/wk, 12 wks	–	Circulating leukocytes, lymphocytes, helper or cytotoxic T cells, NK cells, NKT cells
Sprod et al., 2010	Breast and prostate cancer patients	During radiation therapy	Intervention (n=20); control (n=22)	Aerobic (walking) + resistance exercise (home-based)	Moderate-intensity aerobic + resistance exercise, 4 wks	↓Serum IL-6	Serum TNFα, sTNF-R

Table 2 (*continued*)

Table 2 (*continued*)

Reference	Participants	PA/tumor timeline	Intervention groups	PA modality	PA protocol	Immune outcomes	
						PA effect	PA no effect
Hojan et al., 2017	Prostate cancer patients	During and after radiation therapy (RT)	Intervention (n=35); control (n=31)	Aerobic (treadmill activity or cycling) + resistance exercise	During RT: 30 min aerobic (at 65–70% HRmax) + 25 min resistance training/ session, 5 sessions/ wk, 8 wks; after RT: 40 min aerobic (at 70–80% HRmax) + 35 min resistance training/ session, 3 sessions/ wk,10 months	–	Serum IL-1β, IL-6, TNFα
Battaglini et al., 2009	Acute leukemia patients	During chemotherapy	Pre-post intervention (n=8)	Aerobic (treadmill walking or cycling) + resistance exercise	Aerobic (at 40–50% HRR) + resistance exercise for 30 min total, 2 bouts/day, 3 days/wk, 3–5 wks	↓Serum IL-6	Serum IL-10, IFNγ
Kleckner et al., 2019	Patients of cancer other than leukemia	During chemotherapy	Intervention (n=144); control (n=149)	Aerobic (walking) + resistance exercise	60 min/session aerobic (daily, at 60–85% HRR) and resistance exercise, 6 wks	↓Serum IFNγ, IL-1β	Serum IL-6, IL-8, IL-10, sTNFR1
Fiuza-Luces et al., 2017	Children with solid tumors	During the entire neoadjuvant chemotherapy treatment period	Intervention (n=9); control (n=11)	Aerobic (cycling, treadmill running or arm cranking) + resistance exercise	30 min aerobic (at 60–70% HRmax) + 30 min strength training/ session, 3 sessions/ wk, 17±5 wks	Prevent ↑ in KIR2DS4+ NK cells	Circulating T cells, B cells, NK cells and NK cell subsets; various serum cytokines; NKCC

(III) Post treatment (n=27)

(i) Post treatment – breast cancer (n=18)

Reference	Participants	PA/tumor timeline	Intervention groups	PA modality	PA protocol	PA effect	PA no effect
Giallauria et al., 2014	Breast cancer patients	Within 5 years after mastectomy or conservative surgery	Intervention (n=61); control (n=33)	Aerobic exercise (treadmill activity or cycling)	30 min/session at 70% VO₂max, 3 sessions/ wk for 3 months + 1 session/wk for 9 months, 12 months in total	↓Serum HMGB-1	Serum hsCRP, IL-6

Table 2 (*continued*)

Table 2 (*continued*)

Reference	Participants	PA/tumor timeline	Intervention groups	PA modality	PA protocol	Immune outcomes	
						PA effect	PA no effect
Sturgeon et al., 2018	BRCA1/2[+] breast cancer patients	≥4 months after breast cancer treatment	Intervention (n=20); control (n=22)	Aerobic + resistance exercise¶	3 days/wk aerobic + 3 days/wk resistance exercise, 160 min/wk in total, 12 months	↓Serum IL-6	Serum IL-1β, IL-8, TNFα
Peters et al., 1994	Breast cancer patients	≥6 months after surgery	Pre-post intervention (n=24)	Aerobic exercise (cycling)	5 times/wk for 5 wks + 2–3 times/wk for 6 months, 7 months in total	↑NKCC	Number or percentage of circulating NK cells
Peters et al., 1995	Breast cancer patients	≥6 months after surgery	Pre-post intervention (n=24)	Aerobic exercise (cycling)	30–40 min/day, 5 times/wk for 5 wks + 2–3 times/wk for 6 months	↑%Circulating granulocytes, ↓lymphocytes and monocytes; ↑Monocyte phagocytosis	–
Dethlefsen et al., 2016	Breast cancer patients	Post primary treatment	Intervention (n=37); control (n=37)	Aerobic (cycling) + resistance exercise plus exercise counseling	Supervised exercise 90 min/session, 1 session/wk, 6 months	↓Serum TNFα	Serum IL-6, IL-8, IL-10
Hutnick et al., 2005	Breast cancer patients	≥2 wks after the completion of chemotherapy	Intervention (n=21); control (n=15)	Aerobic (treadmill running, walking) + resistance exercise	20 min aerobic (at 60–75% functional capacity) + resistance training/session, 3 sessions/wk, 3–6 months	↑%Circulating CD4+/CD69+ cells; ↑mitogen-stimulated lymphocyte proliferation	Circulating CD3^{+}, CD4^{+}, CD8^{+} T cells, B cells, NK cells^{+}; IFNγ, IL-6 production by mitogen-stimulated lymphocytes; Plasma IFNγ, IL-6, sIL-6R, sgp130, IFNγ/IL-6 ratio
Dieli-Conwright et al., 2018	Post-menopausal breast cancer patients (BMI ≥30 kg/m²)	After the completion of radiotherapy and/or chemotherapy	Intervention (n=10); control (n=10)	Aerobic + resistance exercise	150 min moderate-vigorous (at 65–80% HRmax) aerobic exercise + 2–3 days of resistance exercise training/wk, 16 wks	↓Plasma CRP, IL-6, IL-8; ↓%M1 and ↑%M2 macrophages, ↑IL-12 in the adipose tissue	–

Table 2 (*continued*)

Table 2 (*continued*)

Reference	Participants	PA/tumor timeline	Intervention groups	PA modality	PA protocol	Immune outcomes	
						PA effect	PA no effect
Fairey et al., 2005	Post-menopausal breast cancer patients	After the completion of surgery, radiotherapy, and/or chemotherapy	Intervention (n=25); control (n=28)	Aerobic exercise (cycling)	15–35 min/session at 70–75% VO₂max, 3 sessions/wk, 15 wks	↑NKCC; ↑spontaneous lymphocyte proliferation	Mitogen-stimulated lymphocyte proliferation; Blood mononuclear cell phenotypes and cytokine production, neutrophil function[†]
Fairey et al., 2005	Post-menopausal breast cancer patients	After the completion of surgery, radiotherapy, and/or chemotherapy	Intervention (n=25); control (n=28)	Aerobic exercise (cycling)	15–35 min/session at 70–75% VO₂max, 3 sessions/wk, 15 wks	↓Serum CRP	–
Rogers et al., 2013	Breast cancer patients	Post primary treatment	Intervention (n=11); control (n=9)	Aerobic + resistance exercise	150 min moderate-intensity aerobic + 2 sessions of resistance training/wk, gradually shifted to home-based exercise, 3 months	–	Serum IL-6, IL-8, IL-10, TNFα, IL-6/IL-10 ratio, IL-6/IL-8 ratio, IL-8/IL-10 ratio, TNFα/IL-10 ratio
Rogers et al., 2014	Post-menopausal breast cancer patients	≥4 wks after final primary treatment administration	Intervention (n=20); control (n=22)	Aerobic (walking) + resistance exercise	Aerobic (40 min/session at 48–52% HRR, 4 sessions/wk) + resistance (2 sessions/wk) exercise, 3 months	↓Serum IL-10	Serum IL-6, IL-8, TNFα, IL-6/IL-10 ratio, IL-8/IL-10 ratio, TNFα/IL-10 ratio
Alizadeh et al., 2019	Non-metastatic and hormone-responsive breast cancer patients	≥1 month after the completion of radiotherapy and/or chemotherapy	Intervention (n=24); control (n=26)	Aerobic exercise (treadmill walking)	38 min/session, at 50–95% HRmax, 3 days/wk, 12 wks	↑Serum TNFα, ↓IL-6, TNFα/IL-10 and IL-6/IL-10 ratio; ↑IL-4 production by mitogen-stimulated PBMCs	Serum IL-10, IL-1β; IFNγ production by mitogen-stimulated PBMCs
Gomez et al., 2011	Post-menopausal breast cancer patients	2 to 5 years post treatment	Intervention (n=8); control (n=8)	Aerobic (cycling) + resistance exercise	20–30 min aerobic (at 70–80% HRmax) + resistance training/session, 3 sessions/wk, 8 wks	Prevent ↑in serum CTACK; ↓Serum IL-15, MIF, IL-10/TNFα ratio	Various serum cytokines

Table 2 (*continued*)

Table 2 (*continued*)

Reference	Participants	PA/tumor timeline	Intervention groups	PA modality	PA protocol	Immune outcomes	
						PA effect	PA no effect
Jones et al., 2013	Post-menopausal breast cancer patients	≥6 months after completion of adjuvant treatment	Intervention (n=36); control (n=32)	Aerobic exercise (primarily walking)	30 min/session at 60–80% HRmax, 5 sessions/wk, 8 wks	–	Serum IL-6, CRP, TNFα
Nieman et al., 1995	Breast cancer patients	Within 4 years after surgery, radiotherapy, and/or chemotherapy	Intervention (n=6); control (n=6)	Aerobic (walking) + resistance exercise	30 min aerobic (at 75% HRmax) + resistance training/session, 3 sessions/wk, 8 wks	–	Number of circulating lymphocytes, neutrophils, T cells, NK cells; NKCC
Tizdast et al., 2016	Breast cancer patients (BMI > 25 kg/m²)	≥6 months after the completion of surgery, radiotherapy, and/or chemotherapy	Continuous EX (n=9); interval EX (n=9); control (n=9)	Aerobic exercise (treadmill acivity)	Continuous (15–40 min at 30–50% THR) or interval (5×3 to 8×5 min at 40–60% THR) exercise, 3 times/wk, 8 wks	–	Serum IL-6, TNFα, hCRP
Karimi et al., 2015	Breast cancer patients (BMI > 25 kg/m²)	Post radiotherapy and/or chemotherapy	Intervention (n=10); control (n=10)	Aerobic exercise (water-based)	20–60 min/session at 50–75% HRR, 4 sessions/wk, 6 wks	↓Serum IL-10, hsCRP	–
Zimmer et al., 2018	Breast cancer patients	During stationary rehabilitation	Pre-post intervention (n=60)	Personalized exercise recommendations	9–15 MET/wk for 3 wks, plus 1-week stays at the clinic 4 and 8 months later	↓Serum CRP	Serum TNFα, IL-6, MIF
(ii) Post treatment—gastrointestinal cancer (n=5)							
Lee et al., 2017	Colorectal cancer patients	Within 4 wks to 2 yrs after completion of surgery, radiotherapy, and/or chemotherapy	Intervention (n=62); control (n=61)	Aerobic + resistance exercise (home-based)	>18 MET h/wk for 6 wks + 27 MET h/wk for 6 wks, 12 wks in total	↓Serum TNFα	Serum hsCRP
Lee et al., 2013	Colorectal cancer patients	After the completion of surgical resection and chemotherapy	Intensely (IIHE) or casually (CIHE) intervened EX (n=17 in total)§	Aerobic + resistance exercise (home-based)	18 MET h/wk for 6 wks + 27 MET h/wk for 6 wks (IIHE) or educational session (CIHE), 12 wks in total	↓Serum TNFα	Serum hsCRP, IL-6

Table 2 (*continued*)

Table 2 (*continued*)

Reference	Participants	PA/tumor timeline	Intervention groups	PA modality	PA protocol	Immune outcomes	
						PA effect	PA no effect
Devin et al., 2019	Colorectal cancer patients	≥1 month after the completion of surgery, radiotherapy, and/or chemotherapy	Pre-post intervention (n=10)	Aerobic exercise (cycling)	38 min/session, at 50–95% HRmax, 3 days/wk, 4 wks	–	Serum TNFα, IL-6, IL-8[†]
Allgayer et al., 2014	Colorectal cancer patients	≥4 wks after the completion of primary treatment	Moderate intensity EX (ME, n=13); low intensity EX (LE, n=10)	Aerobic exercise (cycling)	40 min/day at 55–65% (ME) or 30–40% (LE) of individual aerobic power, 2 wks	–	Circulating and LPS-stimulated IL-1β, IL-6, TNFα, sTNFI/II[†]
Na et al., 2000	Stomach cancer patients	PA initiated from day 2 post curative surgery	Intervention (n=17); control (n=18)	Aerobic exercise (cycling, arm cranking)	30 min/session, 2 sessions/day, 5 days/wk, 2 wks	↑NKCC	–
(iii) Post treatment—other cancers (n=4)							
Hvid et al., 2016	Prostate cancer patients	After radical prostatectomy or during active surveillance	Intervention (n=12); control (n=7)	Aerobic exercise (home-based)	45 min/session at 50–100% VO$_2$max, 3 sessions/wk, 24 months	–	Serum TNFα, IL-6
Ricci et al., 2018	Cancer patients	After the completion of treatment	Pre-post intervention (n=76)	Aerobic (walking or running) + resistance exercise	Aerobic (at 30–85% HRR) + strength training for a total of 60 min/session, 3 sessions/wk, 26 wks	–	Serum CRP
Guinan et al., 2017	Esophageal cancer patients	≥1 year after the completion of curative treatment	Pre-post intervention (n=12)	Aerobic exercise[¶]	Supervised (at 30–60% HRR) and home-based aerobic exercise, 12 wks	↓Serum IL-8	Serum IL-1β, IL-6, TNFα
Glass et al., 2015	Patients with solid tumors	Post definitive surgery	Intervention (n=23); control (n=21)	Aerobic exercise (cycling)	20–45 min/session at 55–100% VO$_2$peak, 3 sessions/wk, 12 wks	↓Serum IL-4, MIP-1β; Prevent ↑ in serum TNFα; ↑Circulating CD4+, CD8+, CD8+/CD45RA T cells	Circulating B cells, NK cells, monocytes

[†], data not shown; [§], both groups increased PA level with no difference between groups, thus results from all participants were combined for analysis; [¶], PA intervention combined with dietary counselling without restriction in caloric intake. ↑, increase (compared to control group or pre-intervention level); ↓, decrease (compared to control group or pre-intervention level). BMI, body mass index; RCT, randomized controlled trial; HIIT, high-intensity interval training; VO$_2$peak, volume of peak oxygen uptake; RPE, rate of perceived exertion; HRR, heart rate reserve; HRmax, maximum heart rate; THR, target heart rate; MET, metabolic equivalent of task; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; hsCRP, high-sensitivity CRP; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MIF, macrophage migration inhibiting factor; HMGB-1, high mobility group box-1 protein; CTACK, cutaneous T cell-attracting chemokine; ICAM, intracellular adhesion molecule; PBMC, peripheral blood mononuclear cell; EX, exercise.

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was also found, while no change was observed in tumor-infiltrating CD4^{+} or CD8^{+} T cells or macrophages.

Effects of ER on cancer immune outcomes

Preclinical findings

Twenty-two studies investigated the effect of ER interventions on cancer immune outcomes using preclinical cancer models (*Table 3*). Two additional studies (120,121) investigating the effects of caloric restriction mimetics (CRMs) on cancer immune outcomes were also included in *Table 3*. Compared to preclinical studies using PA interventions, the ER studies comprised a more diverse group of cancer types, including breast (n=5, 23%) (45,122-125), gastrointestinal (n=5, 23%) (126-130), lung (n=2, 9%) (131,132), liver (n=2, 9%) (133,134), pancreatic (n=2, 9%) (135,136) and several other cancer types (n=6, 27%) (137-142). ER regimens used can be divided into two broad categories: continuous ER and intermittent fasting. Continuous ER was mostly given as a 30–40% reduction in caloric intake, except for two studies where a 5% (131) or 10% (45) reduction in caloric intake was applied, respectively. Intermittent fasting was commonly applied as periodic fasting and refeeding, with the fasting interval ranging from several hours per day to several days per week [different types of ER regimens are reviewed in (143)]. Notably, four studies investigated the effect of ER in comparison to *ad libitum* fed control and obese mice on cancer immune outcomes (128,136-138). In four additional studies, mice were fed a high fat diet to induce obesity, and an ER regimen was implemented to evaluate the effect of ER-induced weight loss in obesity on tumor and immune outcomes (125,130-132). Despite the heterogeneity in study designs, 21 of 22 studies reported positive effects of ER on tumor outcomes including reduced tumor incidence, tumor growth, metastases, and improved survival independent of starting body weight.

Similar to preclinical PA studies, immune outcomes in the preclinical ER studies were commonly assessed in the tumor, spleen and blood. In the spleen, the percentage of T cells was increased in three studies (130,136,139), and T cell proliferation and CTL activity were increased in two studies (45,139) and one study (139), respectively. The percentage of NK cells was unchanged in one study (124), while NK cell cytotoxicity was increased in two studies (124,140) and reduced in one study (139). The percentage and/or number of MDSCs was also reduced in two studies (45,136). The number of total circulating leukocytes and lymphocytes was reduced in two studies (133,140), while increased lymphocyte proliferation was found in another study (141). Among the serum cytokines evaluated, TNFα was reduced in one study (128) and increased in another study (140). IL-6 was reduced in two studies (128,137) and unchanged in one study (127). MCP-1 was reduced in five studies (125,131,132,135,137). IFNγ was increased in one study (140) and unchanged in two studies (127,128). A few studies also assessed immune outcomes in other tissue compartments. One study found an increased percentage of T cells and a reduced percentage of MDSCs in the TDLN (136), and another study reported an increase in the percentage of T cells and macrophages in the non-TDLN (130).

Among the tumor immune infiltrates, the percentage and/or number of T cells was increased in two studies (45,136), reduced in two studies (134,138), and unchanged in one study (122). The percentage and/or number of MDSCs was reduced in two studies (45,136), macrophages was reduced in three studies (129,138,142), and Tregs was unchanged in one study (122). Among the inflammatory cytokines within the tumor, TNFα was increased in one study (126) and reduced in another study (138), IL-6 was reduced in two studies (126,138) and unchanged in one study (123), and IL-1β (126,138) and MCP-1 (126,135) were each reduced in two studies. In addition, two studies reported changes in multiple immune and inflammatory pathways within the TME (45,134).

Apart from the aforementioned studies using dietary ER interventions, two studies investigating the effects of CRMs on cancer immune outcomes were also identified. In one study using an experimental metastasis model (120), CRM administration resulted in a reduction in lung metastasis, concurrently with favorable changes in the immune cell populations and cytotoxic activity in the lung. In the other study (121), CRM had no effect on tumor growth or tumor-infiltrating Tregs when used alone, while it improved the efficacy of chemotherapy with enhanced anti-cancer immunosurveillance.

Clinical findings

Only six clinical studies were identified that investigated the effect of ER on tumor immune outcomes (*Table 4*). All six studies were conducted in cancer patients with overweight or obesity, and weight loss interventions included the combination of PA and ER. Five out of the six studies (144-148) were conducted in breast cancer patients, and one study (149) recruited patients of a mix of cancer types.

Table 3 Preclinical findings on the effects of ER on cancer immune outcomes

Reference	Tumor model	ER regimen	ER/tumor timeline	Tumor outcomes	Immune outcomes ER effect	Immune outcomes ER no effect
(I) Breast cancer (n=5)						
Di Biase et al., 2016	Female BALB/c mice, 4T1 mammary tumor (s.c. inoculation)	4-day fasting-mimicking diet + 10-day ad libitum for every 2 wks	ER initiated 4 days after tumor inoculation and lasted up to 42 days after tumor inoculation	↓Tumor growth	↑Common lymphoid progenitor cells in the bone marrow	Tumor-infiltrating CD8$^+$ T cells, Tregs
Turbitt et al., 2019	Female BALB/c mice, 4T1.2 mammary tumor (orthotopic inoculation)	10% ER (alone or in combination with PA)	ER from 8 wks before to 5 wks after tumor inoculation	↓Tumor growth; ↓lung and femur metastasis; ↑survival (all effects by PA + ER)	↓MDSC accumulation, ↑CD4$^+$ T cell proliferation in the spleen (PA + ER); ↓tumor-infiltrating MDSCs, ↑CD8$^+$ T cells, CD8$^+$:MDSC ratio (PA + ER); altered inflammatory and immune pathways within the tumor	–
Hodgson et al., 1997	Male F344 rats, MADB106 mammary tumor (i.v. inoculation)	Food access restricted to 2 h/day (50% of ad libitum food intake)	ER from 1 wk before to 3 wks after tumor inoculation	↓Lung metastasis	↑Splenic NKCC	%Splenic NK cells
Fernandes et al., 1995	Female MMTV/v-Ha-ras transgenic mice, spontaneous mammary tumor	40% ER	ER initiated at 1 month of age and lasted up to 32 months of age	↓Tumor incidence;↑survival	–	IL-6 gene expression within the tumor
Sundaram and Yan, 2018	Female MMTV-PyMT mice, spontaneous mammary tumor	Control diet ad libitum (Ctrl); high-fat diet ad libitum (HFD); high-fat diet restricted to 12h dark phase (ER)	HFD initiated at 3 wks of age, ER from 4 to 12 wks of age	↓Tumor latency (Ctrl < ER < HFD); ↓Tumor progression (Ctrl/ER < HFD); no change in lung metastasis†	↓Plasma MCP-1 (Ctrl/ER < HFD)	–
(II) Gastrointestinal cancer (n=5)						
Harvey et al., 2013	Female C57BL/6 mice, MC38 colon cancer (s.c. inoculation)	30% ER entirely due to reduced carbohydrates	ER from 22 wks before to 24 days after tumor inoculation	↓Tumor volume	↓IL-6, IL-1β, COX-2, CCL2, F4/80, S100A9, ↑TNFα, Hpgd gene expression within the tumor	–

Table 3 (*continued*)

Table 3 (*continued*)

Reference	Tumor model	ER regimen	ER/tumor timeline	Tumor outcomes	Immune outcomes ER effect	Immune outcomes ER no effect
Sun et al., 2017	Female BALB/c mice, CT26 colon cancer (s.c. inoculation)	Alternate day fasting	ER initiated when tumors were palpable (5–7 days after tumor inoculation) and lasted 2 wks	↓Tumor growth	↓%Tumor-infiltrating M2 macrophages	–
Olivo-Marston et al., 2014	Male FVB mice, AOM-induced colon cancer	Control diet ad libitum (Ctrl); diet-induced obesity (DIO); 30% ER	ER initiated 1 wk after the completion of tumor induction and lasted up to 19 wks	↓Tumor multiplicity (ER < Ctrl < DIO)	↓Serum GM-CSF, IL–1β, IL–4, IL–5, IL–6, TNFα (ER < Ctrl < DIO)	Serum IFNγ, IL-2, IL-10, IL-12
Velazquez et al., 2016	Male C57BL/6 mice, AOM-induced colon cancer	High-fat diet before and after tumor induction (Ctrl); high-fat diet before and low-fat diet after tumor induction (ER)	HFD initiated 20 wks before tumor induction, followed by 30 wks of HFD or LFD feeding	No change in polyp number and size	↑Macrophages, CD4+, CD8+, CD4+/CD69+ T cells in the spleen and mesenteric LN[‡]	DCs in the spleen and mesenteric LN[‡]
Huffman et al., 2013	Male and female Apc[1638/N+] mice, spontaneous intestinal tumor	40% ER	ER initiated at 16 wks of age and lasted 12 wks	↓Number of macroadenoma; ↑survival	↓Serum CXCL-1	Serum IFNγ, IL-10, IL-12, IL-1β, IL-6
(III) Lung cancer (n=2)						
Yan et al., 2019	Male C57BL/6 mice, Lewis lung carcinoma (s.c. inoculation)	Control diet ad libitum (Ctrl); high-fat diet ad libitum (HFD); high-fat diet restricted to 12 h dark phase (ER)	ER initiated 3 wks after the beginning of HFD and 7 wks before tumor inoculation, and lasted until 20 days after tumor inoculation	↓Lung metastasis (Ctrl/HFD < ER)	↓Plasma MCP-1 (Ctrl/ER < HFD)	–
Sundaram and Yan, 2016	Male C57BL/6 mice, Lewis lung carcinoma (s.c. inoculation)	Control diet ad libitum (Ctrl); high-fat diet ad libitum (HFD); high-fat diet with 5% ER	ER initiated 3 wks after the beginning of HFD and 5 wks before tumor inoculation, and lasted until 20 days after tumor inoculation	↓Lung metastasis (Ctrl/ER < HFD); no change in primary tumor weight[†]	↓Plasma MCP-1 (Ctrl/ER < HFD)	–

Table 3 (*continued*)

Table 3 (*continued*)

Reference	Tumor model	ER regimen	ER/tumor timeline	Tumor outcomes	Immune outcomes	
					ER effect	ER no effect
(IV) Liver cancer (n=2)						
Ploeger et al., 2017	Male C57BL/6 mice, DEN-induced hepatocellular carcinoma	30% ER	ER initiated upon tumor induction and lasted 49 wks	↓Tumor number (no visible tumors in ER groups)	↓%Neutrophils and T cells, ↓lobular inflammation, altered gene expression profile in non-transformed liver tissue	–
Molina-Aguilar et al., 2017	Male Wistar rats, DEN-induced hepatocellular carcinoma	Food access restricted to 2 h/day	ER concurrent with tumor induction period (18 wks in total)	↓Neoplastic transformation	↓Number of circulating leukocytes, lymphocytes, monocytes, granulocytes (↓leukocytosis); ↑%circulating lymphocytes	–
(V) Pancreatic cancer (n=2)						
Harvey et al., 2014	Male C57BL/6 mice, Panc.02 pancreatic cancer (s.c. inoculation)	30% ER entirely due to reduced carbohydrates	ER from 21 wks before to 5 wks after tumor inoculation	↓Tumor volume and weight	↓F4/80, CCL2, S100A9 gene expression and NFκB activation within the tumor; ↓serum MCP-1	–
Turbitt et al., 2019	Female C57BL/6 mice, Panc.02 pancreatic cancer (s.c. inoculation)	Control diet *ad libitum* (overweight); high-fat diet *ad libitum* (obese); 30% ER (lean)	Dietary intervention initiated 16 wks before tumor inoculation and lasted 60 days	↓Tumor growth (ER < Ovwt/Obese); ↑survival (ER > Ovwt > Obese)	↑T cell and subsets, ↓MDSC and subsets, ↑CD8⁺:MDSC ratio in the spleen, TDLN and tumor; ↓gene expression of inflammatory and MDSC-associated markers in the adipose tissue	–
(VI) Other cancers (n=6)						
Blando et al., 2011	Male Hi-Myc transgenic mice, spontaneous prostate cancer	Control diet *ad libitum* (overweight); diet-induced obesity (DIO); 30% ER	Dietary intervention initiated at 6-8 wks of age and lasted until 3 or 6 months of age	↓Incidence and severity of adenocarcinoma (ER < Ovwt < DIO)	↓Macrophage and T lymphocytes in the ventral prostate; ↓IL1α, IL1β, IL6, IL7, IL23, IL27, NFκB1, TNFα gene expression in the ventral prostate	–
Al-Wahab et al., 2014	Female C57BL/6 mice, ID8 ovarian cancer (i.p. inoculation)	Control diet (Ctrl); high-fat diet *ad libitum* (HFD); 30% ER	Dietary intervention from 30 days before to 60 days after tumor inoculation	↓Ascites (ER < Ctrl/HFD); ↓tumor number (ER < Ctrl < HFD)	↓MCP-1 and IL-6 in the plasma and ascitic fluid	–

Table 3 (*continued*)

Table 3 (*continued*)

Reference	Tumor model	ER regimen	ER/tumor timeline	Tumor outcomes	Immune outcomes	
					ER effect	ER no effect
Matsuzaki et al., 2000	Male BDF1 mice, L1210 leukemia (i.d. inoculation)	40% ER	ER initiated 4 wks before tumor inoculation and lasted up to 3.5 wks	↓Tumor weight; ↑survival	↓Number of circulating total leukocytes, lymphocytes, neutrophils; ↑plasma IFNγ, TNFα; ↑splenic NKCC	Number of circulating monocytes
Mukhopadhyay et al., 1994	Male Swiss albino mice, Dalton's lymphoma (i.p. injection)	40% ER	ER initiated immediately after tumor inoculation and lasted up to 3.5 wks	↓Tumor growth; ↑survival‡	↑Mitogen-stimulated proliferation by circulating lymphocytes‡; ↑serum IgG and IgM	Peritoneal macrophage cytotoxic activity
Mulrooney et al., 2011	Male C57BL/6 mice, CT-2A astrocytoma (i.c. inoculation)	30% ER	ER initiated 48 h after tumor inoculation and lasted 13 days	↓Tumor weight	↓Gene expression of COX-2, AIF-1, MIP-2 within the tumor; ↓tumor-infiltrating macrophages	Plasma MIP-2
Konno et al., 1991	Male C3H/HeN mice, MC-induced tumor	40% ER	ER from 8 wks before to 114 days after tumor induction	↓Tumor incidence	↑Splenic T cells, CD4+ T cells‡; ↑T cell proliferation‡, CTL activity‡; ↓NKCC‡	–
(VII) Caloric restriction mimetics (n=2)						
Le Noci et al., 2019	Female C57BL/6 mice, B16 melanoma (i.v. inoculation)	CR mimetics (alpha-lipoic acid + spermidine + hydroxycitrate)	CRM administration initiated 1 day after tumor inoculation and lasted 20 days	↓Lung metastasis	↑Alveolar macrophages, DCs; ↑M1 and ↓M2 markers in myeloid cells, ↑T cells, NK cells, and CD69+ cells in the lung; ↑cytotoxic activity of effector cells in the lung	–
Pietrocola et al., 2019	Female C57BL/6 mice, MCA205 fibrosarcoma (s.c. inoculation)	CR mimetic (hydroxycitrate)	CRM administration initiated when tumor area reached 25–35 mm² and lasted up to 30 days after tumor inoculation	No change in tumor growth	–	Tumor-infiltrating Tregs

†, data not shown; ‡, statistical testing not shown. ↑, increase (compared to control group unless otherwise indicated); ↓, decrease (compared to control group unless otherwise indicated). IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; MCP, monocyte chemoattractant protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; MIP, macrophage inflammatory protein; AIF, allograft inflammatory factor; COX, cyclooxygenase; NFκB, nuclear factor κ-light-chain-enhancer of activated B cells; Hpgd, 15-hydroxyprostaglandin dehydrogenase; DC, dendritic cell; NK, natural killer; NKCC, NK cell cytotoxicity; CTL, cytotoxic T cell; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; LN, lymph node; TDLN, tumor-draining lymph node; AOM, azoxymethane; DEN, diethylnitrosamine; MC, 3-methylcholanthrene; s.c., subcutaneous; i.v. intravenous; i.p., intraperitoneal; i.d. intradermal; i.c., intracerebral; CR, caloric restriction.

Table 4 Clinical findings on the effects of weight loss (by PA+ER) on cancer immune outcomes

Reference	Participants	Intervention/ tumor timeline	Intervention groups	Weight loss intervention protocol			Immune outcomes	
				PA intervention	ER intervention	Length	PA + ER effect	PA + ER no effect
Demark-Wahnefried et al., 2019	Breast cancer patients (BMI ≥25 kg/m²)	Before surgery	Intervention (n=17); control (n=15)	Supervised (1–2 sessions/wk) and home-based aerobic exercise	Dietary counseling on ER to achieve an energy deficit of 750–1,000 kcal/day	30 days on average	↑Serum TNFα; ↑TNFα nuclear staining, ↑gene expression of IL-1β, CX3CL1 and CXCL1 in the tumor	Serum IL-6
Pakiz et al., 2011	Breast cancer patients (BMI ≥25 kg/m²)	After the completion of surgery, radiotherapy, and/or chemotherapy	Pre-post intervention (n=44)	PA guidance to achieve ≥1 h/day of moderate-intensity aerobic exercise	Dietary guidance on ER to achieve an energy deficit of 500–1,000 kcal/day	12 months	↓Serum IL-6	Serum TNFα, IL-8
Saxton et al., 2014	Breast cancer patients (BMI >25 kg/m²)	Within 3–18 months after the completion of surgery, radiotherapy, and/or chemotherapy	Intervention (n=44); control (n=41)	30 min aerobic (65–85% HRmax) + 10–15 min resistance exercise/ session, 3 sessions/wk	Individualized hypocaloric healthy eating program to achieve an energy deficit of 600 kcal/ day	24 wks	↑Prevent in circulating leukocytes, neutrophils, lymphocytes, CD4⁺ and CD8⁺ T cells	Circulating monocytes, NK cells; serum IL-6, TNFα; NKCC, mitogen-stimulated lymphocyte proliferation
Campbell et al., 2012	Breast cancer patients (BMI 25–35 kg/m²)	≥3 months after the completion of adjuvant treatment	Pre-post intervention (n=14)	Supervised and home-based aerobic exercise to achieve 150 min/wk of moderate-vigorous PA	Dietary sessions and individually prescribed ER to achieve a 7% loss of baseline body weight	24 wks	–	Serum CRP
Swisher et al., 2015	Breast cancer patients (BMI >25 kg/m²)	≥3 months after the completion of active treatment	Intervention (n=13); control (n=10)	Aerobic exercise (30 min/session at 60–75% HRmax, 5 sessions/wk)	Dietary counseling to achieve 200 kcal/ wk reduction in fat calories	16 wks	–	Serum CRP, IL-6, TNFα
Brown et al., 2018	Patients of hematologic malignancies and solid tumors (BMI >25 kg/m²)	≥1 month after the completion of surgery, radiotherapy, and/or chemotherapy	Intervention (n=30); control (n=30)	Supervised aerobic exercise to achieve 150–200 min/wk of moderate-intensity PA	Dietary recommendations to achieve an energy deficit of 500–1,000 kcal/day	15 wks	–	Serum CRP, IL-6

↑, increase (compared to control group or pre-intervention level); ↓, decrease (compared to control group or pre-intervention level). BMI, body mass index; HRmax, maximum heart rate; IL, interleukin; TNF, tumor necrosis factor; CXCL, CXC chemokine ligand; CX3CL, CX3C chemokine ligand; CRP, C-reactive protein; NKCC, natural killer cell cytotoxicity.

One study (145) assessed the effect of a pre-surgical weight loss intervention on serum and intratumoral immune and inflammatory markers. The remaining five studies applied the weight loss interventions post-cancer treatment and only blood samples were analyzed.

When comparing the serum cytokine levels in the weight loss intervention group to the control, TNFα (145,147,148), IL-6 (145,147-149), and CRP (148,149) were mainly unchanged. When comparing post-intervention to pre-intervention, TNFα (146) and CRP (144) were unchanged in one study, while IL-6 was reduced in one study (146). Circulating immune cells were compared between the intervention group and the control in one study (147). The weight loss intervention prevented an increase in the number of circulating lymphocytes and neutrophils over time, while no effect on monocytes, NK cell number or cytotoxicity, or lymphocyte proliferation was found after weight loss.

Immune outcomes within the tumor were assessed in one study (145). A weight loss intervention conducted prior to surgery resulted in an altered gene expression profile in the tumor, including an upregulation of multiple pathways associated with immune function, notably genes encoding IL-1β, and the chemokines CX3CL1 and CXCL1. In addition, genes associated with cytolytic CD56^{dim} NK cells were also positively correlated with weight loss.

Discussion

In the current study, we evaluated preclinical and clinical studies investigating the effects of PA and ER on cancer immune outcomes. To our knowledge, this is the first review to assess the existing evidence on the effects of energy balance-related interventions on host immune responses across the cancer continuum.

PA preclinical findings

Abundant evidence from epidemiological studies suggest that PA is associated with reduced cancer risk, mortality and recurrence, with the strongest evidence found in breast and colon cancer (3-7). As a result, much attention has been paid to these two cancer types in both preclinical and clinical studies investigating the effect of PA interventions on cancer immune outcomes. Consistent with the findings reported in epidemiological studies, the majority of preclinical studies included in this review reported a beneficial effect of PA on tumor incidence, progression, metastasis and survival. However, existing evidence on the effect of PA on cancer

immune outcomes is highly heterogeneous. A wide range of immunological parameters has been assessed from multiple tissue compartments, yet each parameter is usually assessed by a small number of studies with mixed findings.

Because PA is a systemic intervention involving multiple organ systems, changes in systemic immune responses may underlie the beneficial effects of PA on cancer. Studies evaluating splenic immunity mostly focused on NK cells, with two (77,80) and three (62,79,80) reports on increased NK cell percentage/number and cytotoxicity, respectively. In the circulation, a reduction in inflammatory cytokines TNFα, IL-6 and MCP-1 was observed in a few studies (65,68,70,72,74), while several other studies (58,59,68,78) reported no change in serum inflammatory cytokines.

The TME harbors immune cells and molecules directly interacting with the tumor cells. Alterations in these factors may have a significant impact on tumor progression. Existing evidence suggests that PA may result in an increase in anti-tumor effector cells (T cells and NK cells) (44,45,73) and a reduction in pro-tumor immunosuppressive cells (Tregs and MDSCs) (45,61,73) within the TME. However, two studies also reported null results for these cell types (57,58). In addition, several studies found an increase in the percentage of CD8$^+$/IFNγ$^+$ cells in the TDLN (77) and enhanced lymphocyte proliferation from the non-TDLN in physically active hosts (55,56,76), suggesting a PA-induced enhancement in effector cells against the tumor.

Two studies reported global changes in the gene expression profile of immune and inflammatory mediators within the TME (44,45). In the B16 melanoma model, voluntary wheel running increased gene expression of both pro- and anti-inflammatory cytokines as well as NK cell markers, potentially promoting an inflammatory TME and activation of subsequent anti-tumor immune response (44). In the 4T1.2 mammary tumor model, voluntary wheel running, when combined with mild (10%) ER, reduced the expression of chemokines important in MDSC and Treg recruitment, as well as other immune inhibitory molecules (45), including programmed death protein 1 (PD-1) and indoleamine 2,3-dioxygenase (IDO) (150,151). Furthermore, both studies observed an increase in T cell infiltration into tumors in physically active animals. Despite the differences in these cancer models, findings from these two studies suggest that PA may be reshaping the TME to allow greater anti-tumor immune response with less immunosuppression.

It is worth noting that the interpretation of existing evidence may be confounded by the heterogeneity in

the study design of the PA interventions, including the modality, frequency, intensity and duration of each PA session, as well as the total length of the intervention period and the window of PA intervention in relation to cancer treatment. Several studies examined the effect of PA modality, intensity or length of intervention on cancer and immune outcomes, but overall there was insufficient data to determine what intervention protocols may be the most effective in improving cancer and immune outcomes.

PA clinical findings

Despite the heterogeneity in the design of PA interventions, most clinical studies reported no effect of PA on serum inflammatory cytokines and circulating immune cells. This is the case regardless of when the PA intervention occurred with respect to cancer treatment. In contrary to our findings, a recent meta-analysis by Khosravi et al. (49) reported that exercise training decreases circulating pro-inflammatory markers, notably CRP and TNF, in cancer survivors. However, this meta-analysis included studies performing all types of structured exercise intervention (aerobic, resistance or combined training or Tai Chi/yoga), while we focused on the effect of chronic, aerobic PA in the current study. Additionally, Khosravi et al. assessed the effects of exercise training only post-treatment in adult cancer survivors, while we included studies with cancer patients during all stages of treatment. It may be that the type of activity intervention and time since cancer treatment are important variables influencing the relationship between activity and circulating cytokines.

In humans, the effect of PA on immune outcomes within the tumor has not been explored in many studies. Only one study evaluated a pre-surgical PA intervention in breast cancer patients and demonstrated that PA resulted in an upregulation in multiple pathways involved in immune cell function and inflammatory signaling within the TME (94). These results are consistent with preclinical findings and suggest that PA may have a significant impact on the immune response within the tumor. However, additional studies are needed to confirm these findings.

ER preclinical findings

The effect of ER on cancer outcomes has mostly been studied in preclinical cancer models. Despite the heterogeneity in study designs, the preclinical studies included in this review consistently reported beneficial effects of ER on tumor incidence, progression, metastasis and survival in normal weight hosts. Four studies investigated the effect of ER, a control diet fed ad libitum and feeding a high fat diet to induce obesity in different cancer models (128,136-138). All demonstrated that tumor outcomes are improved by ER and exacerbated by obesity. An additional four studies (125,130-132) evaluated the effect of ER in obese mice. In three of these studies (125,131,132), ER reduced tumor progression or lung metastasis in obese mice to the level observed in normal weight mice. These results suggest that ER may have a beneficial effect on cancer outcomes in both normal weight and obese hosts.

Similar to the PA intervention studies, preclinical ER intervention studies have also assessed a wide variety of immunological parameters, while each parameter is usually assessed by a small number of studies with mixed findings. ER increases the percentage of splenic T cells (130,136,139) and their function (proliferation and CTL activity) (45,139). Splenic MDSC accumulation was also reduced in two studies (45,136). In addition, serum MCP-1 was reduced in five studies (125,131,132,135,137), while other circulating inflammatory cytokines were reported with mixed results.

Existing evidence suggests that ER may reduce inflammation and immunosuppression within the TME. The inflammatory cytokines IL-1β, IL-6 and MCP-1 in the tumor were reduced by ER in several studies (126,135,138). The percentage of tumor-infiltrating MDSCs was also reduced in two studies (45,136), suggesting that ER may reduce immune suppression both systemically and within the TME. ER in combination with PA resulted in global changes in the gene expression profile within the 4T1.2 mammary tumor, notably a downregulation of an array of genes involved in immune suppression (45). Similar findings were reported in a carcinogen-induced liver cancer model, where a 30% ER prevented hepatic tumor formation while downregulating multiple pathways involved in inflammation (134). Overall, preclinical studies evaluating the effects of ER on cancer immune outcomes also present a mix of positive and null findings. Some evidences suggest that ER may prevent an immunosuppressive TME and induce favorable changes in splenic effector vs. immunosuppressive cells.

ER clinical findings

To date, all clinical studies applying ER interventions have been conducted in cancer patients with overweight or obesity with the purpose of weight loss. The weight

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loss intervention in all six included studies combined PA with ER, thus precluding the ability to make conclusions regarding the efficacy of each intervention alone on immune outcomes. Despite the limited number of studies, evaluation of serum inflammatory cytokines mostly resulted in null findings. This suggests that, similar to PA interventions, weight loss by the combination of PA+ER may not have a significant impact on cancer immune response in the circulation. In the study by Demark-Wahnefried *et al.* (145), a weight loss intervention prior to surgery altered the gene expression profile within the TME, represented by an upregulation of multiple pathways associated with immune function. These results support the hypothesis that PA and ER interventions may be modulating the immune response within the TME, but additional studies are needed to examine this issue.

ER regimens may not be tolerated or feasible for cancer patients. Thus, CRMs have been explored. CRMs mimic the biochemical effects of nutrient deprivation without drastic changes in the calorie content of the diets, and have anti-tumor effects in several preclinical studies (152). While most studies attribute their beneficial effects to the induction of autophagy, emerging evidence also suggests that CRMs may improve anti-cancer immune surveillance when used alone or in combination with chemotherapy (120,121). In the current preclinical evidence base, intermittent fasting is as effective as chronic ER in improving tumor and immune outcomes, and may prove to be another alternative to prolonged dietary ER in cancer patients. Using a preclinical cancer model, we have shown that the combination of PA and 10% ER is as effective as a single 30–40% ER intervention in reducing tumor progression and improving survival. Furthermore, the combination of PA and mild ER induces beneficial changes in multiple immune mechanisms to a greater extent than either intervention alone (45). Thus, by combining lifestyle interventions such as PA with ER, we may be able to use a less severe ER regimen to improve cancer outcomes.

One limitation of the current review is that the included studies are highly heterogeneous in terms of cancer type, animal model or human participant characteristics, and the PA or ER protocol. There are also limitations inherent to the included human studies. A number of the human studies are exploratory trials with small sample size, and some are not powered for immune outcome measures. In addition, patient adherence to the PA and/or ER interventions varied from 66–98% in the included studies. Thus, limited conclusions can be made as to the role of PA and ER on cancer-related immune outcomes.

Conclusions and future directions

There is mounting interest in the effect of energy balance-related lifestyle interventions on cancer immune responses. Preclinical studies clearly suggest a beneficial effect of PA and ER on tumor outcomes. However, little is known about which immune mechanisms may be the most important contributor to the improved tumor outcomes observed in response to either PA or ER interventions. Further mechanistic studies are warranted to better understand the relationship between energy balance-related interventions, improved cancer outcomes, and host immune responses. To this end, we recommend the use of more clinically relevant cancer models, including orthotopic tumor transplantation and spontaneous tumor development in genetically-engineered animals. The impact of different PA and ER protocols should also be carefully evaluated to inform clinical application. As such, standardized reporting of the intervention protocols [such as those proposed by Ashcraft *et al.* (32)] is encouraged.

Existing clinical evidence suggest against a significant impact of PA or ER on circulating inflammatory cytokines, while emerging evidence from both preclinical and clinical studies suggest that PA and ER may significantly alter the immune and inflammatory milieu within the TME. Future studies that examine the immunological changes within the TME in response to PA and/or ER may provide valuable insight into the relevant immune pathways that may be altered. In addition, previous clinical studies have primarily assessed the effect of PA and ER interventions post-cancer treatment. Additional studies are needed to evaluate the effect of PA and ER performed prior to, or concurrently with cancer treatment to determine if a critical window exists where energy balance-related interventions may result in maximal benefit. Because PA and ER target the two components of the energy balance equation (energy expenditure and energy intake, respectively), it would also be interesting to assess if any additive or synergistic effects exist between PA and ER on cancer immune regulation. Finally, several studies demonstrate that PA and ER may enhance the efficacy of chemotherapy (121,122,153), while no studies, to our knowledge, have assessed the effect of PA and/or ER on immunotherapy outcomes. Future studies are needed to determine if ER and/or PA could be used in combination with standard or experimental therapies to improve clinical outcomes.

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Footnote

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Table S1 Search strategy

(I) PubMed

("exercise"[mesh] OR "exercise"[tiab] OR "exercises"[tiab] OR "physical activity"[tiab] OR "physical activities"[tiab] OR "physical fitness"[mesh] OR "physical fitness"[tiab] OR "aerobic activity"[tiab] OR "aerobic activities"[tiab] OR "aerobic training"[tiab] OR "endurance training"[tiab] OR "physical endurance"[tiab] OR "physical conditioning"[tiab] OR "walk"[tiab] OR "walking"[tiab] OR "swim"[tiab] OR "swimming"[tiab] OR "running"[tiab] OR "jog"[tiab] OR "jogging"[tiab] OR "cardiovascular activity"[tiab] OR "cardiovascular activities"[tiab] OR "cardiometabolic"[tiab]

OR

"caloric restriction"[mesh] OR "caloric restriction"[tiab] OR "calorie restriction"[tiab] OR "low calorie diet"[tiab] OR "low-calorie diet"[tiab] OR "low calorie diets"[tiab] OR "low-calorie diets"[tiab] OR "diet restriction"[tiab] OR "dietary restriction"[tiab] OR "energy restriction"[tiab] OR "weight loss"[mesh] OR "weight loss"[tiab] OR "weight losses"[tiab] OR "weight-loss"[tiab] OR "weight-losses"[tiab] OR "weight reduction"[tiab] OR "weight reductions"[tiab] OR "fasting"[mesh] OR "fasting"[tiab] OR "intermittent fasting"[tiab] OR "intermittent fastings"[tiab] OR "time restricted feeding"[tiab] OR "time restricted feedings"[tiab] OR "time-restricted feeding"[tiab] OR "time-restricted feedings"[tiab])

AND

("immune"[tiab] OR "immunity"[mesh] OR "immunity"[tiab] OR "immune system"[mesh] OR "immune system phenomena"[mesh] OR "immunotherapy"[mesh] OR "immunotherapy"[tiab] OR "immunotherapies"[tiab] OR "leukocyte"[tiab] OR "leukocytes"[tiab] OR "lymphocyte"[tiab] OR "lymphocytes"[tiab] OR "T cell"[tiab] OR "T cells"[tiab] OR "B cell"[tiab] OR "B cells"[tiab] OR "natural killer"[tiab] OR "NK cell"[tiab] OR "NK cells"[tiab] OR "monocyte"[tiab] OR "monocytes"[tiab] OR "macrophage"[tiab] OR "macrophages"[tiab] OR "dendritic cell"[tiab] OR "dendritic cells"[tiab] OR "neutrophil"[tiab] OR "neutrophils"[tiab] OR "myeloid-derived suppressor cells"[mesh] OR "myeloid-derived suppressor cell"[tiab] OR "myeloid-derived suppressor cells"[tiab] OR "myeloid derived suppressor cell"[tiab] OR "myeloid derived suppressor cells"[tiab] OR "regulatory T cell"[tiab] OR "regulatory T cells"[tiab] OR "Treg"[tiab] OR "Tregs"[tiab] OR "immunosuppression"[tiab] OR "antigen presentation"[tiab] OR "cytokine"[tiab] OR "cytokines"[tiab] OR "chemokine"[tiab] OR "chemokines"[tiab] OR "antibodies"[mesh] OR "antibody"[tiab] OR "antibodies"[tiab] OR "immunoglobulins"[mesh] OR "immunoglobulin"[tiab] OR "immunoglobulins"[tiab] OR "inflammation"[mesh] OR "inflammation"[tiab] OR "inflammations"[tiab] OR "inflammatory"[tiab])

AND

("neoplasms"[mesh] OR "neoplasms"[tiab] OR "neoplasm"[tiab] OR "neoplasia"[tiab] OR "neoplasias"[tiab] OR "cancer"[tiab] OR "cancers"[tiab] OR "tumor"[tiab] OR "tumors"[tiab] OR "tumour"[tiab] OR "tumours"[tiab] OR "malignancy"[tiab] OR "malignancies"[tiab])

NOT review[pt]

AND English[lang]

(II) Web of Science

TOPIC: ("exercise" OR "exercises" OR "physical activity" OR "physical activities" OR "physical fitness" OR "aerobic activity" OR "aerobic activities" OR "aerobic training" OR "endurance training" OR "physical endurance" OR "physical conditioning" OR "walk" OR "walking" OR "swim" OR "swimming" OR "running" OR "jog" OR "jogging" OR "cardiovascular activity" OR "cardiovascular activities" OR "cardiometabolic"

OR

"caloric restriction" OR "calorie restriction" OR "low calorie diet" OR "low-calorie diet" OR "low calorie diets" OR "low-calorie diets" OR "diet restriction" OR "dietary restriction" OR "energy restriction" OR "weight loss" OR "weight losses" OR "weight-loss" OR "weight-losses" OR "weight reduction" OR "weight reductions" OR "fasting" OR "intermittent fasting" OR "intermittent fastings" OR "time restricted feeding" OR "time restricted feedings" OR "time-restricted feeding" OR "time-restricted feedings")

AND

TOPIC: ("immune" OR "immunity" OR "immunotherapy" OR "immunotherapies" OR "leukocyte" OR "leukocytes" OR "lymphocyte" OR "lymphocytes" OR "T cell" OR "T cells" OR "B cell" OR "B cells" OR "natural killer" OR "NK cell" OR "NK cells" OR "monocyte" OR "monocytes" OR "macrophage" OR "macrophages" OR "dendritic cell" OR "dendritic cells" OR "neutrophil" OR "neutrophils" OR "myeloid-derived suppressor cell" OR "myeloid-derived suppressor cells" OR "myeloid derived suppressor cell" OR "myeloid derived suppressor cells" OR "regulatory T cell" OR "regulatory T cells" OR "Treg" OR "Tregs" OR "immunosuppression" OR "antigen presentation" OR "cytokine" OR "cytokines" OR "chemokine" OR "chemokines" OR "antibody" OR "antibodies" OR "immunoglobulin" OR "immunoglobulins" OR "inflammation" OR "inflammations" OR "inflammatory")

AND

TOPIC: ("neoplasm" OR "neoplasms" OR "neoplasia" OR "neoplasias" OR "cancer" OR "cancers" OR "tumor" OR "tumors" OR "tumour" OR "tumours" OR "malignancy" OR "malignancies")

AND

LANGUAGE: English

NOT

DOCUMENT TYPES: Review

(III) CENTRAL

ti.ab.kw.: ("exercise" OR "physical activity" OR "aerobic activity" OR "aerobic training" OR "endurance training" OR "caloric restriction" OR "calorie restriction" OR "dietary restriction" OR "energy restriction" OR "weight loss" OR "weight reduction")

AND

ti.ab.kw.: ("immune" OR "immunity" OR "immunotherapy" OR "leukocyte" OR "lymphocyte" OR "T cell" OR "B cell" OR "natural killer" OR "NK cell" OR "monocyte" OR "macrophage" OR "dendritic cell" OR "neutrophil" OR "myeloid-derived suppressor cell" OR "cytokine" OR "chemokine" OR "antibody" OR "immunoglobulin" OR "inflammation" OR "inflammations" OR "inflammatory")

AND

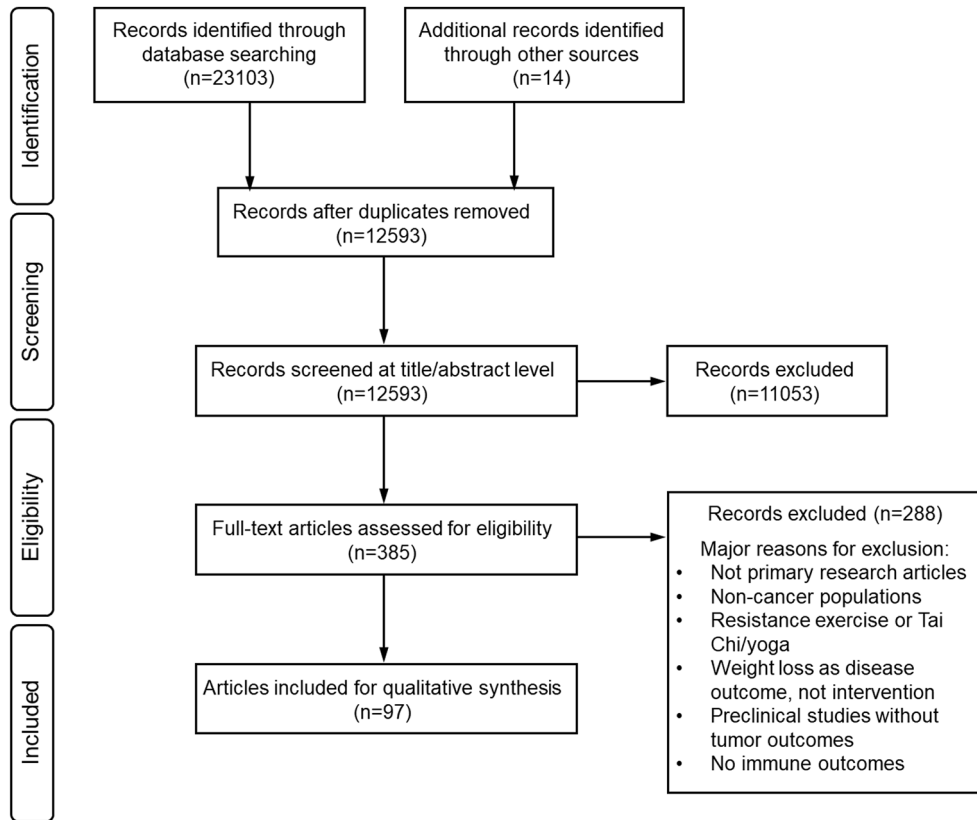ti.ab.kw.: ("neoplasm" OR "neoplasia" OR "cancer" OR "tumor" OR "malignancy")

Figure S1 PRISMA flow diagram of the study selection process.