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Review

Suppressive effects of exercise-conditioned serum on cancer cells: A narrative review of the influence of exercise mode, volume, and intensity

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Abstract

Cancer is a major cause of morbidity and mortality worldwide, and the incidence is increasing, highlighting the need for effective strategies to treat this disease. Exercise has emerged as fundamental therapeutic medicine in the management of cancer, associated with a lower risk of recurrence and increased survival. Several avenues of research demonstrate reduction in growth, proliferation, and increased apoptosis of cancer cells, including breast, prostate, colorectal, and lung cancer, when cultured by serum collected after exercise *in vitro* (i.e., the cultivation of cancer cell lines in an experimental setting, which simplifies the biological system and provides mechanistic insight into cell responses). The underlying mechanisms of exercise-induced cancer suppressive effects may be attributed to the alteration in circulating factors, such as skeletal muscle-induced cytokines (i.e., myokines) and hormones. However, exercise-induced tumor suppressive effects and detailed information about training interventions are not well investigated, constraining more precise application of exercise medicine within clinical oncology. To date, it remains unclear what role different training modes (i.e., resistance and aerobic training) as well as volume and intensity have on exercise-conditioned serum and its effects on cancer cells. Nevertheless, the available evidence is that a single bout of aerobic training at moderate to vigorous intensity has cancer suppressive effects, while for chronic training interventions, exercise volume appears to be an influential candidate driving cancer inhibitory effects regardless of training mode. Insights for future research investigating training modes, volume and intensity are provided to further our understanding of the effects of exercise-conditioned serum on cancer cells.

Keywords: Cancer cells; High intensity interval training; Moderate intensity continuous training; Resistance training; Myokines

1. Introduction

The importance of exercise for promoting general well-being, maintaining good health, and even as a form of medical treatment has been an increasingly popular topic of research over the past decades. In recognition of the effects of exercise, the World Health Organization has provided exercise recommendations specifically for the management of noncommunicable diseases, including cardiovascular disease, chronic respiratory disease, type 2 diabetes mellitus, and cancer.[1,2] The World Health Organization expert panel recommends at least 150–300 min or 75–150 min of moderate to vigorous aerobic activity per week respectively, along with strengthening exercises at moderate to high intensity twice per week, to prevent the onset of noncommunicable diseases.[1,3,4] Among these diseases, cancer represents a significant contributor to both morbidity and mortality worldwide, with breast, lung, colorectal, and prostate cancer being the leading causes of cancer-related deaths (10 million deaths in 2020).[5] Unfortunately, the incidence of cancer is increasing worldwide, highlighting the need for effective strategies to prevent and treat this disease.[5]

Exercise has emerged as a novel and fundamental therapeutic intervention in the management of cancer, as supported by multiple studies.[6–9] Indeed, a robust body of evidence now exists on the safety and effectiveness of exercise as medicine,

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either during or post-cancer treatments, to improve various health-related cancer outcomes, such as fatigue, quality of life, cardiorespiratory capacity, neuromuscular strength, physical function, body weight, and body composition (both fat mass and lean mass), as well as the ability to alleviate symptoms of anxiety and depression.[10–14] Furthermore, exercise is associated with a lower risk for the development of a range of cancers as well as reduced recurrence and improved survival in patients with cancer.[15–17] The underlying mechanisms are not yet fully understood; however, over the past 2 decades, several avenues of preclinical and clinical research have investigated the effects of acute and chronic exercise-conditioned serum on different cancer cell lines *in vitro* (e.g., breast, prostate, and colon). Briefly, this novel methodology involving direct application of the serum obtained from human subjects/patients before and after exercise to a cultured-controlled environment with cancer cell lines (*in vitro* experiments) revealed that exercise-conditioned serum had inhibitory effects on cancer cell growth (i.e., proliferation and metastatic capacity) and survival (i.e., viability), as well as increased cell death (i.e., apoptosis and necrosis).[18–22] This methodology may partially provide the underlying biological reasons for the association between exercise and reduced recurrence or improved survival in patients with cancer, as well as reveal some of the potential molecular candidates. The underlying reasons come from the fact that previous *in vitro* studies pointed out how altered circulating factors (e.g., insulin-like growth factor-1 (IGF-1) in obese subjects) may drive cancer cell growth, which was subsequently confirmed in mechanistic experiments in co-culture systems and, lastly, validated in human subjects.[23,24] Accordingly, *in vitro* experiments can be employed for therapeutic interventions in the translational continuum from basic discovery to clinical outcomes.

It has been postulated that exercise alters the concentrations of hormones (e.g., insulin, IGF-1), adipokines (e.g., leptin, adiponectin), and cytokines (e.g., tumor necrosis factor alpha (TNF-α)),[25–28] which are considered to be factors associated with tumorigenesis.[29–31] Notably, among them, myokines (e.g., interleukin 6 (IL-6), secreted protein rich in cysteine (SPARC)), which are cytokines released into the systemic circulation in response to muscular contractions, have been demonstrated to potentially suppress cancer cell growth, proliferation, and increase apoptosis in different cancer cell lines in several *in vitro* studies.[32–41] These findings are encouraging, and myokines may be an attractive area for future investigations.

Given the novelty of exercise as medicine, experimental studies have been conducted in both healthy individuals and cancer patients with the aim of collecting blood following both acute and chronic training interventions and culturing it *in vitro* with cancer cells. It has been reported that exercise-conditioned serum suppresses cancer cell growth, proliferation as well as increases apoptosis in breast, prostate, colon, and lung cancers.[42–47] Notably, the magnitude of such effects on circulating factors (e.g., myokines) and cancer cells have varied in blood collected immediately after exercise (i.e., acute effects) compared to that taken at rest (i.e., chronic effects) to avoid the arousal effects of exercise.[42,44,45,48] When it comes to the type of exercise undertaken, 2 distinct modes have been commonly used: resistance training (RT) and aerobic training (AT).[8] The purpose of RT is to elicit muscle hypertrophy and improve muscular strength,[49,50] whereas AT is to improve cardiorespiratory fitness and metabolic health.[51] AT can be performed as moderate intensity continuous training (MICT) or high intensity interval training (HIIT).[52,53] Although these training modes have different physiological pathways, both have been commonly used in exercise oncology.[8]

However, it remains unclear which type of training mode (i.e., RT *vs.* AT), along with associated volume and intensity, is more effective in altering circulating factors (i.e., hormones, cytokines, and myokines), which then have suppressive effects on cancer cells. Thus, the aim of the current review was to critically examine which training mode, volume, and intensity have been adopted in different populations to alter blood contents, which in turn have suppressive effects on cancer cells. To the best of our knowledge, no reviews have been conducted to critically examine such training parameters. Additionally, we present directions for future research that may provide critical insight into the practice of exercise medicine for patients with cancer.

2. Methods

Empirical research studies and review journal articles were retrieved from electronic databases of MEDLINE, PubMed, Scopus, and CINHAL databases. Of note, our search strategy did not exclude previously published review articles (like many systematic reviews do) because our goal was to conduct a narrative review on a substantially under-researched topic. Thus, review articles served as a useful source for any articles that were not found in our initial searches. The search strategy combined specific terms with the words: “cancer”, “serum”, and “exercise” to ensure relevant articles were extracted. The search terms included: “cancer OR tumor OR neoplasm AND exercise OR physical activity OR resistance training OR aerobic training AND serum AND growth OR proliferation OR viability OR apoptosis”. Articles were deemed relevant after scanning the title and abstract and where subsequent access to the full text was available from the relevant publishers. The reference lists of each study were also checked to ensure no further articles were omitted from the search process. All searches were conducted between February and April 2023.

As a result, only studies in breast, prostate, colorectal, and lung cancers conducted in subjects with and without cancer were found. Such studies examined the effects of the exercise-conditioned serum on cancer cells and are discussed in the following sections followed by directions for future research. It should be noted that all cancer patients in the reviewed studies were either undergoing primary cancer treatments (e.g., chemotherapy, hormone therapy, radiotherapy) or were in the survivorship phase, during which exercise was applied as adjuvant therapy.

3. Breast cancer

Breast cancer is the most diagnosed cancer worldwide;[5,54] thus, several studies have been conducted to examine the effects of circulating factors (e.g., myokines) on breast cancer cells in preclinical studies, and with promising results.[39–41,55–57] Recently, studies have been conducted in both healthy individuals and patients with breast cancer. However, and somewhat surprisingly, there remains a lack of studies investigating the effects of exercise-conditioned serum on breast cancer cells.

3.1. Studies in subjects without breast cancer

The effects of exercise-conditioned serum on breast cancer cells have been investigated in subjects without cancer. For example, in regard to the acute effects (i.e., single bout of exercise) of exercise-conditioned serum, Dethlefsen et al.[42] examined MICT performed at 55% maximal oxygen uptake (VO_{2max}) for 2 h on a cycle ergometer in 7 healthy women (Table 1). Serum acquired 1−2 h post exercise resulted in a significant decrease in the viability (i.e., the ability of cancer cells to survive, grow, and maintain cellular function) of breast cancer cell lines MCF-7 by 10%−19% and MDA-MB-231 by 13%−14% ($p < 0.05$). Thus, preliminary evidence shows that an acute bout of exercise at 55% VO_{2max}, which corresponds to approximately 70% maximum heart rate (HR_{max}),[58] may suppress breast cancer cell growth. Similarly, Baldelli et al.[59] investigated the effects of a high intensity endurance test to exhaustion (i.e., up to 90% maximal power (P_{max})) in 12 healthy women before and after a 9-week HIIT protocol performed 3−4 days a week. They reported that exercise-conditioned serum taken before commencing the HIIT protocol (i.e., acute) inhibited MDA-MB-231 cell proliferation by 12.1%−24.9% in the untrained state (with serum acquired immediately after to 24 h after the endurance test to exhaustion) ($p < 0.05$). Interestingly, suppressive cancer cell proliferation effects were greater when applying the serum (collected at the same time points mentioned above) after the 9-week HIIT protocol (i.e., MDA-MB-231 cell proliferation decreased by 15.7%−35.3%; $p < 0.05$). Regarding the circulating factors, the authors examined only levels of creatine kinase, finding a transient increase immediately after exercise. The high intensity (i.e., 90% P_{max}) appears to mediate the inhibitory response of breast cancer cells after the incremental test. Additionally, suppressive cancer effects were even greater after a 9-week HIIT protocol, highlighting how the weekly training volume selected increased the capacity of the exercise-conditioned serum to inhibit breast cancer cell proliferation. This supports the contention that exercise training interventions not only have inhibitory effects due to acute exercise bouts but also that the systemic changes that occur with chronic training have tumor suppressive effects.

Barnard et al.[22] investigated a short-term diet and exercise program in 38 overweight and obese post-menopausal women (Table 2). Participants received a low-fat and high-fiber diet in addition to 30−60 min MICT (i.e., treadmill) at 70%−85% HR_{max} 4−5 days a week and 40−60 min <70% HR_{max} 1−2 days a week for 2 weeks. Resting serum levels of IGF-1 (−19%), IGF-binding protein-1 (IGFBP-1) (+32%), insulin (−29%), and estradiol (−37% to −34%) significantly improved after 2 weeks ($p < 0.05$). When examining the effects on breast cancer cell lines, the exercise-conditioned serum significantly reduced *in vitro* MCF-7 cell growth by 6.6%, ZR-75-1 by 9.9%, and T-47D by 18.5%, as well as increased apoptosis of the breast cancer cell lines MCF-7 by 23%, ZR-75-1 by 20%, and T-47D by 30% ($p < 0.05$). Interestingly, blood was collected in a resting state, showing that even a short-term training program had positive effects on hormones and cancer cell growth. This may be related to the high volume of exercise used (i.e., >5 days per week), even though it is unknown which component (i.e., diet or exercise) contributed most to these effects.

3.2. Studies in patients with breast cancer

The first acute study in patients with breast cancer was reported by Dethlefsen and colleagues,[43] who examined the effects of a single bout consisting of a 30-min warmup, RT for 60 min, and 30 min of HIIT on a stationary cycle ergometer at 80%−85% HR_{max} in 20 overweight breast cancer patients undergoing chemotherapy half-way through a 6-week supervised training intervention (Table 3). Significant increases in IL-6 (+110%), IL-8 (+20%), TNF-α (+13%), lactate (+500%), epinephrine (+190%), and norepinephrine (+120%) were found in the serum collected immediately after the acute session which, in turn, resulted in significant decreases in MCF-7 and MDA-MB-231 cell viability, by 9.2% and 9.4%, respectively ($p < 0.05$). This was in accordance with another study led by the same research group using the same cohort where MCF-7 and MDA-MB-231 cell viability significantly decreased, by 11% and 9%, respectively ($p < 0.05$).[42] Notably, the mixed approach (i.e., RT plus HIIT) resulted in significant positive alterations in blood content taken immediately after the acute exercise session. However, it is unclear whether changes were induced by the training volume (i.e., 2 h) and/or intensity (i.e., >70% HR_{max}) or by different training stimuli (i.e., RT *vs.* HIIT).

In contrast, results differed when Dethlefsen et al.[43] investigated the chronic effects of a 6-month training intervention once per week compared to a control group in 74 breast cancer survivors (Table 4). The training intervention comprised RT, including 3 sets of 8−10 repetitions for major muscle groups (e.g., leg press, knee extension, chest press, *etc.*) at 70%−90% 1 repetition maximum (RM), plus HIIT based on work bouts of 30 s to 6 min at 80%−90% HR_{max} on a stationary cycle ergometer. The control group received 3 health evaluation consultations. Exercise resulted in a significant decrease in resting levels of IL-6 (Intervention = −37%; Control = −20.7%), TNF-α (Intervention = −21.1%), and low-density lipoprotein/high-density lipoproteins (Intervention = −18.2%; Control = −11.4%) after 6 months ($p < 0.05$), while no changes were observed in IL-8, IL-10, insulin, leptin, or glucose levels. When examining the effects of exercise-conditioned serum on MCF-7 and MDA-MB-231 breast

Table 1
Summary of acute exercise studies in subjects without cancer.

Cancer	Subject	Training intervention	Blood sampling	Circulating factor	Exercise effect (pre *vs.* post)	Setting and cancer cell line	Effects on cancer cells
Breast	Healthy female (age = 24 (year), BMI = 23 (kg/m^2))[42]	INT ($n = 7$): single bout of MICT (at 55% VO_{2max} on stationary cycle ergometer) for 2 h under supervision	Pre: resting; post: 1 h and 2 h after exercise	IL-6 Lactate Epinephrine Norepinephrine	↑* (2.4-fold) ↑* (1.5-fold) ↑* ↑	Serum exercise *in vitro* on breast cancer cell MCF-7 and MDA-MB-231	*Pre vs. post serum 1 h after*: MCF-7 cell viability ↓* by 10%; MDA-MB-231 cell viability ↓* by 14%; *Pre vs. post serum 2 h after*: MCF-7 cell viability ↓* by 19%; MDA-MB-231 cell viability ↓* by 13% at 48 h
	Healthy female (age = 21, BMI = 21)[59]	INT ($n = 12$): HIEC (incremental test from 50% to 90% P_{max} up to exhaustion on stationary cycle ergometer)	Pre: 2 h fasting; post: immediately after, 4 h and 24 h after exercise	CK	Immediately after: ↑; 4 and 24 h: N/C	Serum exercise *in vitro* on breast cancer cell MDA-MB-231	*Pre vs. post serum immediately after*: MDA-MB-231 cell proliferation ↓* by 12.1%; *Pre vs. post serum 4 h after*: MDA-MB-231 cell proliferation ↓* by 24.0%; *Pre vs. post serum 24 h after*: MDA-MB-231 cell proliferation ↓* by 24.9%
Prostate	Healthy male (age = 25, BW = 58−82 kg)[20]	INT ($n = 10$): single bout of MICT (20 min at 50% VO_{2max}, 40 min at 65% VO_{2max} on stationary cycle ergometer)	Pre: resting; post: 2 h after exercise	IGFBP-1 EGF Cortisol IGF-1	↑ (35%) ↓ (18%) N/C N/C	Serum exercise *in vitro* on prostate cancer cell LNCaP	*Pre vs. post*: LNCaP cell growth ↓* by 31% at 96 h; LNCaP proliferation ↓* at 48 h; LNCaP apoptosis N/C at 24 and 48 h
	Healthy male (young group: age = 28, BMI = 23; old group: age = 63, BMI = 25)[65]	INT ($n = 20$): single bout of MICT (20 min at 50% VO_{2max}, 40 min at 65% VO_{2max} on stationary cycle ergometer)	Pre: fasting; post: immediately after exercise	IL-6 IL-15 Irisin OSM SPARC Testosterone	NA NA NA ↑* ↑* ↑* (young); ↑ (old)	Serum exercise *in vitro* on prostate cancer cell LNCaP and PC3	*Pre vs. post young*: LNCaP metabolic activity N/C; PC3 metabolic activity N/C; LNCaP cell number N/C; PC3 cell number N/C; *Pre vs. post old*: LNCaP metabolic activity ↓*; PC3 metabolic activity N/C; LNCaP cell number N/C; PC3 cell number N/C at 24 and 48 h
	Healthy male (age = 21, BMI = 22)[59]	INT ($n = 18$): HIEC (incremental test from 50% to 90% P_{max} up to exhaustion on stationary cycle ergometer)	Pre: 2 h fasting; post: immediately after, 4 h and 24 h after exercise	CK	Immediately after: ↑; 4 and 24 h: N/C	Serum exercise *in vitro* on prostate cancer cell LNCaP	*Pre vs. post serum immediately after*: LNCaP cell proliferation ↓* by 13.8%; *Pre vs. post serum 4 h after*: LNCaP cell proliferation ↓* by 21.8%; *Pre vs. post serum 24 h after*: LNCaP cell proliferation ↓* by 22.8%
Colorectal	Healthy male (age = 60, BMI = 30)[73]	INT ($n = 8$): single bout of MIIT (6 sets × 5 min at 60% $HR_{reserve}$, 2.5 min active recovery, on stationary cycle ergometer) for 60 min; CON ($n = 8$): rest	Pre: before exercise (NA); post: immediately after exercise	IL-6 IL-8 IL-10 TNF-α Irisin OSM SPARC	*INT vs. CON and Pre vs. post* ↑ * (24.6%) N/C NA N/C NA N/C N/C	Serum exercise *in vitro* on colon cancer cell LoVo	*Pre vs. post INT*: LoVo cell proliferation ↓* by 4.2%; *Pre vs. post CON*: LoVo cell proliferation ↑* by 5.4%; *INT vs. CON*: LoVo cell proliferation ↓* by 5.7% at 48 h

(*continued on next page*)

Table 1 (Continued)

Cancer	Subject	Training intervention	Blood sampling	Circulating factor	Exercise effect (pre *vs.* post)	Setting and cancer cell line	Effects on cancer cells
Lung	Healthy male (age = 22, BMI = 24)[47]	INT ($n = 23$): single bout of HIIT (6 sets, 1 min at $90\%_{max}$ workload, and 1 min active recovery on stationary cycle ergometer)	Pre: before exercise (NA); post: 5 min, 1 h and 24 h after exercise	IL-6	5 min after: ↑ *; 1 and 24 h: N/C	Serum exercise *in vitro* on lung cancer cell A549, H460, and H1299	*Pre vs. post serum 5 min after*: A549 cell proliferation ↓* by 90%; *Pre vs. post serum 1 h after*: A549 cell proliferation ↓* by 91%; *Pre vs. post serum 24 h after*: A549 cell proliferation ↓* by 84%; *Pre vs. Post serum 5 min after*: A549 survival rates ↓* by 21.5%; H460 survival rates ↓* by 37.7%; H1299 survival rates ↓* by 33.5%; *Pre vs. post serum 1 h after*: A549 survival rates ↓* by 33.9%; H460 survival rates ↓* by 38.4%; H1299 survival rates ↓* by 41.9%; *Pre vs. post serum 24 h after*: A549 survival rate survival rates ↓* by 35.8%; H460 survival rates ↓* by 39.3%; H1299 survival rates ↓* by 37.7% at 7 days
				IL-1β	5 min after: ↑ *; 1 and 24 h: N/C		
				IL-1α	5 min after: ↑ *; 1 and 24 h: N/C		
				IL-10	5 min after: ↑; 1 and 24 h: N/C		
				TNF-α	5 min after: ↑*; 1 and 24 h: N/C		

Note: ↑ = increase; ↓ = decrease.

* $p < 0.05$.

Abbreviations: BMI = body mass index; BW = bodyweight; CK = creatine kinase; CON = control; EGF = epidermal growth factor; HIEC = high intensity endurance cycling; HIIT = high intensity interval training; HR = heart rate; IGF-1 = insulin-like growth factor 1; IGFPB = insulin-like growth factor-binding protein; IL = interleukin; INT = intervention; MICT = moderate intensity continuous training; MIIT = moderate intensity interval training; NA = not available; N/C = no changes; OSM = oncostatin M; P_{max} = maximal power; SPARC = secreted protein rich in cysteine; TNF-α = tumor necrosis factor alpha; VO_{2max} = maximal oxygen uptake.

cancer cell lines, no substantial effects were found on cancer cell viability. However, the low volume of training intervention (i.e., 1 day per week) may have been a factor limiting potential adaptations, as highlighted by lack of significant changes in most of the circulating factors (i.e., IL-8, IL-10, insulin, leptin). This was compounded by a training session attendance of only 66%, which is unlikely to be sufficient for maximizing adaptations when training volume is already low.

In summary, it appears that exercise can positively impact circulating factors and that it suppresses cancer cell growth in breast cancer cells. In regard to the acute sessions, preliminary findings show that MICT, HIIT, and mixed (RT plus HIIT) approaches suppressed cancer cell viability and proliferation, with volume up to 2 h and an intensity ranging from moderate to high (i.e., >50% VO_{2max}, 50%−90% P_{max}, 85% HR_{max}).[42,43,59] In both short-term and chronic training interventions (i.e., 11 days and 9 weeks, respectively), adopting 30−60 min of MICT or HIIT, at >70% HR_{max}, at least 3 days per week suppressed cancer cell growth and proliferation,[22,59] while a 90-min moderate to high RT plus HIIT (i.e., 70%−90% 1RM and 80%−90% HR_{max}) for 6 months, once per week, did not inhibit cancer cell viability, although the potential limitations mentioned above should be considered.[43]

4. Prostate cancer

Prostate cancer is the most diagnosed cancer among men,[60] and a number of preclinical studies exploring the effects of circulating factors (e.g., myokines) on cancer cells have shown their suppressive role in various prostate cancer cell lines.[33,34,61−64] This provides the rationale for examining such potential effects in human subjects and the effects of exercise-conditioned serum on prostate cancer cells.

4.1. Studies in subjects without prostate cancer

Similar to breast cancer, several studies have been conducted to assess whether exercise-conditioned serum from subjects without cancer suppresses prostate cancer cell lines. For the acute effects, Rundqvist et al.[20] determined that a single bout of MICT in 10 healthy male subjects cycling for 20 min at 50% of VO_{2max} and for another 40 min at 65% of VO_{2max} significantly decreased the proliferation and growth of prostate cancer cell line LNCaP by 31% ($p < 0.05$), while there was no substantial change in apoptosis (Table 1). The exercise-conditioned serum acquired 2 h post exercise revealed a decrease in epidermal growth factor (EGF) (−18%) and an increase in IGFBP-1 (+35%) compared to the baseline. Moreover, Hwang et al.[65] replicated the training protocol by Rundqvist et al.[20] in 12 young and 10 old male subjects, reporting that SPARC and oncostatin M (OSM) significantly increased after exercise ($p < 0.05$). However, when determining the effects on the cell lines LNCaP and PC3, researchers found that only LNCaP metabolic activity in the older group significantly decreased ($p < 0.05$), while LNCaP and PC3 cell numbers were not affected by the exercise-conditioned serum. Such results were in contrast to previous findings,[20,42] meaning that it needs to be further investigated if

Table 2
Summary of chronic exercise studies in subjects without cancer.

Cancer	Subject	Training intervention	Blood sampling	Circulating factor	Exercise effect	Setting and cancer cell line	Effects on cancer cells
Breast	Overweight and obese post-menopausal female (age = 51−79 (year), BMI = 30 to 32 (kg/m^2), n = 28 on HT)[22]	INT (n = 38): MICT (30−60 min at 70%−85% HR$_{max}$ on treadmill 4−5 days/week; 40−60 min <70% HR$_{max}$ 1−2 days/week) + low fat high fiber diet for 2 weeks under supervision	Pre: overnight fasting; post: overnight fasting	IGFBP-1 IGF-1 Insulin Estradiol	*Pre vs. post* ↑ * (32%) ↓ * (19%) ↓ * (29%) ↓ * (34%−37%)	Serum exercise *in vitro* on breast cancer cell MCF-7, T-47D and ZR-75-1	*Pre vs. post*: MCF-7 cell growth ↓* by 6.6%; ZR-75-1 cell growth ↓* by 9.9%; T-47D cell growth ↓* by 18.5%; MCF-7 apoptosis ↑* by 23%; ZR-75-1 apoptosis ↑* by 20%; T-47D apoptosis ↑* by 30% at 48 h
	Healthy female (age = 21, BMI = 21)[59]	INT (n = 12): HIIT (3−4 days/week) for 9 weeks and HIEC (incremental test from 50% to 90% P$_{max}$ up to exhaustion on stationary cycle ergometer) after the last session	Pre: 2 h fasting; post: immediately after, 4 h and 24 h after exercise	CK	*Pre vs. post* Immediately after: ↑; 4 and 24 h: N/C	Serum exercise *in vitro* on breast cancer cell MDA-MB-231	*Pre vs. post serum immediately after*: MDA-MB-231 cell proliferation ↓* by 15.7%; *Pre vs. post serum 4 h after*: MDA-MB-231 cell proliferation ↓* by 30.6%; *Pre vs. post serum 24 h after*: MDA-MB-231 cell proliferation ↓* by 35.3%
Prostate	Overweight male (age = 59, BMI = 29)[21]	INT1 (n = 13): MICT (30−60 min at 70%−85% HR$_{max}$ on treadmill 4−5 days/week; 40−60 min <70% HR$_{max}$ 1−2 days/week) for 11 days; INT2 (n = 8): MICT (60 min, daily) + low fat high fiber diet for 14 years; CON (n = 7)	Pre: 12 h fasting; post: 12 h fasting	Testosterone Cholesterol LDL HDL Triglycerides Glucose	*Pre vs. post in INT and INT vs. CON* ↓* ↓* ↓* N/C ↓* ↓*	Serum exercise *in vitro on prostate cancer cell* LNCaP	*Pre vs. post INT1*: LNCaP cell growth ↓* by 30%; *Pre vs. post INT2*: LNCaP cell growth ↓ * by additional 15%; *Pre vs. post CON*: LNCaP cell growth N/C at 48 h
	Obese male (age = 60, BMI = 38)[66]	INT1 (n = 14): MICT (60 min, daily) + low fat high fiber diet for 11 days; INT2 (n = 8): MICT (60 min, daily) + low fat high fiber diet for 14 years	Pre: 12 h fasting; post: 12 h fasting	IGF-1 IGFBP-1 IGFBP-3 Insulin	*Pre vs. post INT1* ↓* (20%) ↑* (53%) N/C ↓	Serum exercise *in vitro* on prostate cancer cell LNCaP	*Pre vs. post INT1*: LNCaP cell growth ↓* by 30%; LNCaP apoptosis ↑*; LNCaP necrosis ↑; *Pre vs. post INT2*: LNCaP cell growth ↓* by additional 14%; LNCaP apoptosis ↑* at 48 h
	Healthy (INT1: age = 55, BMI = 21.5; INT 2: age = 62, BMI = 26.5) and obese male (CON: age = 60, BMI = 38)[18]	INT1 (n = 8): MICT (30−60 min at 70%−85% HR$_{max}$ on treadmill 4−5 days/week; 40−60 min < 70% HR$_{max}$ 1−2 days/week) + low fat high fiber diet for 11 days following a regimen for 14 years; INT2 (n = 12): continuous and strenuous calisthenic and swimming laps for 50 min 5 days/week following a regimen for 10 years; CON (n = 14)	Post: overnight fasting	IGFBP-1 IGF-1 Insulin IGFBP-1	*INT1 vs. INT2 vs. CON* ↑ * ↓ * ↓ * *INT1 vs. INT2* ↑ *	Serum exercise *in vitro* on prostate cancer cell LNCaP	*INT1 and INT2 vs. CON*: LNCaP cell growth ↓*; LNCaP apoptosis ↑*; *INT1 vs. INT2*: LNCaP apoptosis ↑* at 48 h
	Healthy (INT: age = 60, BMI = 26) and overweight male (CON: age = 62, BMI = 31)[67]	INT (n = 12): continuous and strenuous calisthenic and swimming laps for 50 min 5 days/week following a regimen for 10 years; CON (n = 10)	Post: overnight fasting	IGFBP-1 IGF-1 Insulin	*INT vs. CON* ↑* ↓* ↓*	Serum exercise *in vitro* on prostate cancer cell LNCaP	*INT vs. CON*: LNCaP cell growth ↓* by 27%; LNCaP apoptosis ↑* by 371% at 48 h
	Healthy male (age = 21, BMI = 22)[59]	INT (n = 18): HIIT (3−4 days/week) for 9 weeks and HIEC (incremental test from 50%−90% P$_{max}$ up to exhaustion on stationary cycle ergometer) after the last session	Pre: 2 h fasting; post: immediately after, 4 h and 24 h after exercise	CK	*Pre vs. post* Immediately after: ↑; 4 h and 24 h: N/C	Serum exercise *in vitro* on prostate cancer cell LNCaP	*Pre vs. post serum immediately after*: LNCaP cell proliferation ↓* by 14.0%; *Pre vs. post serum 4 h after*: LNCaP cell proliferation ↓* by 22.9%; *Pre vs. post serum 24 h after*: LNCaP cell proliferation ↓* by 27.2%

Note: ↑ = increase; ↓ = decrease.

* $p < 0.05$.

Abbreviations: BMI = body mass index; CK = creatine kinase; CON = control; HDL = high-density lipoprotein; HIEC = high intensity endurance cycling; HIIT = high intensity interval training; HR = heart rate; HR$_{max}$ = maximum heart rate; HT = hormone therapy; IGF-1 = insulin-like growth factor 1; IGFPB = insulin-like growth factor-binding protein; INT = intervention; LDL = low-density lipoprotein; MICT = moderate intensity continuous training; N/C = no changes; P$_{max}$ = maximal power.

Table 3
Summary of acute exercise studies in patients with cancer.

Cancer	Subject	Training intervention	Blood sampling	Circulating factor	Exercise effect (pre *vs.* post)	Setting and cancer cell line	Effects on cancer cells
Breast	Breast cancer patients undergoing chemotherapy (age = 49 (year), BMI = 26 (kg/m^2))[43]	INT ($n = 20$): single bout of warmup for 30 min + RT for 60 min + HIIT (at 80%−85% HR_{max} on stationary cycle ergometer) for 30 min under supervision (whole session >70% HR_{max})	Pre: 2 h fasting; post: immediately after exercise	IL-6 IL-8 IL-10 TNF-α Insulin Lactate Epinephrine Norepinephrine	↑* (110%) ↑* (20%) N/C ↑* (13%) N/C ↑* (500%) ↑* (190%) ↑* (120%)	Serum exercise *in vitro* on breast cancer cell MCF-7 and MDA-MB-231	*Pre vs. post*: MCF-7 cell viability ↓* by 9.2%; MDA-MB-231 cell viability ↓* by 9.4% at 48 h
	Breast cancer patients undergoing chemotherapy (age = 49, BMI = 26)[42]	INT ($n = 20$): single bout of warmup for 30 min + RT for 60 min + HIIT (at >80% HR_{max} on stationary cycle ergometer) for 30 min under supervision	Pre: resting; post: immediately after exercise	Epinephrine Norepinephrine	↑* ↑*	Serum exercise *in vitro* on breast cancer cell MCF-7 and MDA-MB-231	*Pre vs. post*: MCF-7 cell viability ↓* by 11%; MDA-MB-231 cell viability ↓* by 9% at 48 h
Prostate	Metastatic castrate-resistant prostate cancer patients (age = 67, BMI = 30)[48]	INT ($n = 9$): single bout of HIIT (6 sets × 4 min at 70%−85% HR_{max} or RPE 7−8, 2 min active recovery at 50%−65% HR_{max} or RPE 5−6 on stationary cycle ergometer) for 40 min under supervision	Pre: 2 h fasting; post: immediately after and 30 min after exercise	SPARC OSM IL-6 IL-15 Decorin Irisin IGF-1	Immediately after: ↑* (19.9%); 30 min: N/C Immediately after: ↑* (11.5%); 30 min: N/C Immediately after: ↑* (10.2%); 30 min: N/C Immediately after: ↑* (7.8%); 30 min: N/C Immediately after: ↑; 30 min: N/C Immediately after: ↑; 30 min: N/C Immediately after: ↑; 30 min: N/C	Serum exercise *in vitro* on prostate cancer cell DU145	*Pre vs. post serum immediately after*: DU145 total cell growth ↓* by 9.67% and 16.93% at 48 and 72 h; *Pre vs. post serum 30 min after*: DU145 total cell growth ↓* by 4.91%, 6.91% and 8.82% at 24, 48, and 72 h
Colorectal	Colorectal cancer survivors (age = 67, BMI = 28)[44]	INT ($n = 10$): single bout of HIIT (4 sets × 4 min at 85%−95% HR_{max}, 3 min active recovery on stationary cycle ergometer) for 38 min	Pre: fasting state; post: immediately after and 2 h after exercise	IL-6 IL-8 TNF-α Insulin	Immediately after: ↑* (44.8%); 2 h: N/C Immediately after: ↑* (24.7%); 2 h: N/C Immediately after: ↑* (15.2%); 2 h: N/C Immediately after: ↑* (38.8%); 2 h: ↓*	Serum exercise *in vitro* colorectal cancer cell CaCo-2 and LoVo	*Pre vs. post serum immediately after*: CaCo-2 cell number ↓* (ES range: −1.7 to −1.1); LoVo cell number ↓* (ES range: − 1.2 to −0.8); CaCo-2 and LoVo apoptosis N/C; *Pre vs. post serum 2 h after*: CaCo-2 and LoVo cell number N/C at 24 h, 48 h, and 72 h

Note: ↑ = increase; ↓ = decrease.

* $p < 0.05$.

Abbreviations: BMI = body mass index; ES = effect size; HIIT = high intensity interval training; HR = heart rate; HR_{max} = maximum heart rate; IGF-1 = insulin-like growth factor-1; IL = interleukin; INT = intervention; N/C = no changes; OSM = oncostatin M; RPE = rating of perceived exertion; RT = resistance training; SPARC = secreted protein rich in cysteine; TNF-α = tumor necrosis factor alpha.

Table 4
Summary of chronic exercise studies in patients with cancer.

Cancer	Subject	Training intervention	Blood sampling	Circulating factor	Exercise effect	Setting and cancer cell line	Effects on cancer cells
Breast	Breast cancer survivors (age = 47 (year), BMI = 24 (kg/m^2))[43]	INT ($n = 37$): RT (8–10 reps and 3 sets at 70%–90% 1RM of leg press, knee extension, chest press, pull down, abdominal crunch, and lower back extension) + HIIT (30 s to 6 min at 80%–90% HR_{max} on stationary cycle ergometer) for 90 min under supervision, 1 day/week for 6 months + individual and group counseling 1–2 h every 2–3 months; CON ($n = 37$): 3 health evaluation consultations	Pre: 8 h overnight fasting; post: 8 h overnight fasting		*INT vs. CON and pre vs. post*	Serum exercise *in vitro* on breast cancer cell MCF-7 and MDA-MB-231	*INT vs. CON* and *Pre vs. post*: MCF-7 and MDA-MB-231 cell viability N/C at 48 h
				IL-6	↓* (INT = 37%; CON = 20.7%)		
				IL-8	N/C		
				IL-10	N/C		
				TNF-α	↓* (INT = 21.1%)		
				Insulin	N/C		
				Leptin	N/C		
				Glucose	N/C		
				LDL/HLD	↓* (INT = 18.2%; CON = 11.4%)		
Prostate	Prostate cancer patients on active surveillance (age = 63, BMI = 29)[69]	INT ($n = 26$): HIIT (5–8 sets × 2 min at 85%–95% VO_{2max}, 2 min active recovery at 40% VO_{2max} on treadmill) for 40 min 3 days/week for 12 weeks under supervision; CON ($n = 26$)	Pre: 12 h fasting; post: 12 h fasting		*Pre vs. post INT*	Plasma exercise *in vitro* on prostate cancer cell LNCaP	*INT vs. CON*: LNCaP cell growth ↓* by 5.1% at 48 h
				PSA	↓*		
				Testosterone	↑		
					Pre vs. post CON		
				PSA	N/C		
				Testosterone	N/C		
	Prostate cancer patients on ADT (age = 73, BMI = 33)[46]	INT ($n = 10$): RT (6–12 RM and 1–4 sets of 5–9 exercises for major muscle groups of the upper and lower body) under supervision, 3 days/week + MICT (at RPE 3–8) self-directed daily for 12 weeks, 2 consultations with dietician to induce caloric deficit of 500–1000 kcal per week + 40 gr whey protein supplement	Pre: 10 h overnight fasting; post: 48 h after exercise		*Pre vs. post*	Serum exercise *in vitro* on prostate cancer cell DU145	*Pre vs. post*: DU145 total cell growth ↓*; DU145 mean cell index ↓* by 21.3%; DU145 average growth rate ↓* by 22.5% at 72 h
				Irisin	NA		
				Decorin	N/C		
				IL-6	NA		
				IL-15	NA		
				SPARC	↑		
				OSM	↑*		
				Myostatin	NA		
				IGF-1	N/C		
				IGFBP-3	↓*		
				IGF-1/IGFBP-3	N/C		
	Metastatic castrate-resistant prostate cancer patients (age = 72–76, BMI = 28–31)[45]	INT ($n = 13$): RT (6–12 RM and 1–5 sets of 6 exercises for major muscle groups of the upper and lower body) + HIIT (6 sets × 60 s at RPE 8) under supervision 2 days/week; MICT (30–40 min at RPE 6, cycling or walking) for 40 min under supervision 1 day/week for 6 months; CON ($n = 12$): self-directed exercise ACSM guidelines	Pre: 10 h overnight fasting; post: 48 h after exercise		*INT vs. CON*	Serum exercise *in vitro* on prostate cancer cell DU145	*INT vs. CON:* DU145 total cell growth ↓* by 20% at 0–72 h; DU145 adjusted mean cell index ↓* at 0–24 h, 24–48 h, 48–72 h
				Irisin	NA		
				Decorin	N/C		
				IL-6	NA		
				IL-15	NA		
				SPARC	↑*		
				OSM	↑*		
				Myostatin	NA		
				IGF-1	N/C		
				IGFBP-3	N/C		
				IGF-1/IGFBP-3	N/C		
Colorectal	Colorectal cancer survivors (age = 65, BMI = 30)[44]	INT ($n = 10$): HIIT (4 sets × 4 min at 85%–95% HR_{max}, 3 min active recovery on stationary cycle ergometer) for 40 min 3 days/week for 4 weeks	Pre: resting and fasting; post: resting and fasting state		*Pre vs. post*	Serum exercise *in vitro* colorectal cancer cell CaCo-2 and LoVo	*Pre vs. post*: CaCo-2 and LoVo cell number N/C at 24, 48, and 72 h
				IL-6	N/C		
				IL-8	N/C		
				TNF-α	N/C		
				Insulin	N/C		
				Glucose	N/C		
				IGF-1	N/C		

Note: ↑ = increase; ↓ = decrease.
* $p < 0.05$.
Abbreviations: ACSM = American College of Sports Medicine; ADT = androgen deprivation therapy; BMI = body mass index; CON = control; HDL = high-density lipoprotein; HIIT = high intensity interval training; HR = heart rate; HR_{max} = maximum heart rate; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; IL = interleukin; INT = intervention; LDL = low-density lipoprotein; MICT = moderate intensity continuous training; N/C = no changes; PSA = prostate specific antigen; RM = repetition maximum; RPE = rating of perceived exertion; RT = resistance training; TNF-α = tumor necrosis factor alpha; VO_{2max} = maximal oxygen uptake.

a single bout of MICT at moderate intensity (i.e., 50%−65% VO_{2max}) is sufficient stimulus for cancer suppressive effects. Additionally, Baldelli et al.[59] utilized a high intensity endurance test to exhaustion in 18 healthy male subjects and reported a reduction in LNCaP proliferation by 13.8%−22.8% ($p < 0.05$), while exercise-conditioned serum taken after a 9-week HIIT program resulted in a reduction in LNCaP by 14.0%−27.2% ($p < 0.05$), which was in line with findings on breast cancer cell lines previously found by the same research group.[59]

Tymchuk and colleagues[21] investigated the effects of MICT plus a low-fat, high-fiber diet in 13 overweight subjects compared to a control group (i.e., 7 subjects) for 11 days (short-term); additionally, serum was also taken from 8 men who had been compliant with the aforementioned diet and exercise regimen for 14 years (long-term) (Table 2). The MICT consisted of 30−60 min of walking on a treadmill with intensity between 70% and 85% HR_{max} (4−5 days a week) and 40−60 min with intensity <70% HR_{max} (1−2 days a week). When LNCaP was cultured with resting serum taken after the last training session in the short-term group, cancer cell growth was significantly reduced by 30% ($p < 0.05$), while no changes were observed in the control group. Additionally, a further 15% growth reduction was found when culturing LNCaP cells with serum taken from men in the long-term group ($p < 0.05$). Similarly, Ngo et al.[66] collected blood from 14 obese subjects before and after an 11-day MICT and low-fat diet protocol (short-term) as well as from 8 men who had followed a similar long-term intervention (i.e., 14 years). They reported a significant decrease in IGF-1 (−20%; $p < 0.05$) and insulin, and an increase in IGFBP-1 (+53%; $p < 0.05$) following the 11-day intervention. LNCaP cancer cell growth was significantly reduced by 30% *in vitro,* with increased apoptosis ($p < 0.05$) and cell necrosis with short-term training serum compared to baseline serum. Interestingly, an additional increase in apoptosis and reduction in cell growth by 14% was found when culturing LNCaP cells with serum obtained from the long-term intervention ($p < 0.05$), which corroborates findings from the previous investigation.[21]

Furthermore, Barnard et al.[18] compared the exercise and diet protocol adopted by Tymchuk et al.[21] (i.e., MICT plus a low-fat, high-fiber diet for 11 days) *vs.* exercise only in 20 healthy men who had participated for at least 10 years in a University adult fitness program *vs.* 14 obese subjects (control group). The exercise only group differed in their training regimen, as subjects performed flexibility activities followed by calisthenics and swimming laps for 1 h for 5 days a week. However, it should be noted that in the exercise only group, training volume and intensity were not reported, which impeded comparisons between groups to be drawn. Importantly, blood was collected at 1 time point only, after the training interventions. Both intervention groups had significantly lower insulin and IGF-1 levels and higher IGFBP-1 ($p < 0.05$), which was also significantly higher in the exercise and diet group compared to the exercise only group ($p < 0.05$). In addition, the exercise and diet intervention resulted in greater effects on the number of apoptotic cells compared to exercise alone ($p < 0.05$), while both interventions were approximately equal in their suppressive effects on LNCaP cell growth compared to the control group. Similarly, Leung et al.[67] examined 12 overweight men who participated for at least 10 years in the aforementioned flexibility, calisthenics, and swim training compared to a control group of 10 men who were obese with sedentary lifestyle and poor dietary habits with blood taken at rest. Insulin and IGF-1 were significantly lower in the intervention group, while IGFBP-1 was significantly higher in the intervention group compared to the controls ($p < 0.05$). LNCaP cell growth was significantly reduced by 27% and apoptosis increased by 371% in the intervention compared to the control group ($p < 0.05$). However, as mentioned above, training parameters were not reported. Collectively, it can be inferred that a high volume of AT or mixed training over a relatively short period was effective in altering hormones and inhibiting cancer cell growth, which is in line with previous breast cancer research,[22] and, furthermore cancer suppressive effects were greater when individuals were compliant with a long-term training program (i.e., >10 years). However, it is still to be determined to what extent diet intervention impacted tumor suppressive effects.[18,21,66]

4.2. Studies in patients with prostate cancer

The first acute intervention study conducted in patients with prostate cancer was done by our group. We investigated the effects of a single bout of HIIT that comprised 6 sets of 4 min at an intensity between 70% and 85% HR_{max} (rating of perceived exertion (RPE) 7−8 on the 1−10 scale) with 2 min of active recovery (50%−65% HR_{max}; RPE 5−6) in 9 obese patients with advanced metastatic castrate resistance prostate cancer who had completed at least 12 weeks of exercise in the INTERVAL-GAP4 trial (Table 3).[48,68] We reported a significant increase ($p < 0.05$) in circulatory SPARC (+19.9%), OSM (+44.8%), IL-6 (+10.2%), and IL-15 (+7.8%) as well as a trend towards an increase in decorin and irisin immediately after the single bout of exercise compared to pre-exercise and returning to baseline level after 30 min of rest. With the serum acquired immediately after the HIIT, total cell growth of the prostate cancer cell line DU145 was reduced by 9.7%−16.9% ($p < 0.05$), while with the serum acquired 30 min after, reduction in total cancer cell growth was between 4.9% and 8.8% compared to baseline serum ($p < 0.05$). Interestingly, it appears that serum collected immediately after exercise had greater effects on total cell growth compared to serum collected 30 min after.

In regard to chronic training interventions, Kang et al.[69] investigated the effects of a 12-week HIIT *vs.* control in 52 overweight prostate cancer patients on active surveillance. The training intervention comprised 5−8 sets of 2 min at high intensity (i.e., 85%−95% VO_{2max}) and 2 min of active recovery (i.e., 40% VO_{2max}) treadmill exercise for approximately 30−40 min, 3 days per week (Table 4). Significant reductions in prostate specific antigen were found in the HIIT group compared to controls ($p < 0.05$), and testosterone increased only in the intervention group. Furthermore, when examining the effects on LNCaP, cancer cell growth was suppressed by −5.1% in HIIT compared to the control condition.

Subsequently, we investigated the effects of combined RT and MICT for 12 weeks in 10 obese patients on androgen deprivation therapy (ADT).[46] RT ranged from 1 to 4 sets of 6−12 RM under supervision 3 days a week, while the MICT was self-directed daily (RPE 3−8 on the 1−10 scale) to achieve 300 min per week of exercise. Resting levels of myokines SPARC and OSM increased ($p < 0.05$), while IGFBP-3 levels decreased ($p < 0.05$) in resting serum from pre- to post-intervention; no meaningful changes were observed in decorin, IGF-1, or IGFBP-3/IGF-1 ratio. When the exercise-conditioned serum after 12 weeks was applied *in vitro* to the prostate cancer cell line DU145, a significant decrease of 22.5% was observed in total cancer cell growth rate, and the mean Cell Index (i.e., the estimated record of cell morphology or cell adhesion) decreased by 21.3% ($p < 0.05$) after incubating the cells with collected serum for 72 h. This was the first study to demonstrate an increase in resting myokine levels with suppressive effects on cancer cells in patients with cancer after a longer-term training intervention (i.e., 12 weeks). This may result from the high training volume selected (i.e., 300 min per week) and the intensity for RT and MICT, which led to significant improvements in body weight, fat mass, and lean mass percentage, and muscle strength ($p < 0.05$).

A similar approach was undertaken when we examined the effects of a 6-month intervention compared to controls in 25 overweight and obese patients with advanced metastatic castrate resistance prostate cancer.[45] The intervention group performed RT (6−12 RM, 2−5 sets) plus HIIT (6 × 60 s at RPE 8) 2 days per week, and 30−40 min of MICT (RPE 6) 1 day per week. The control group was only advised of the current American College of Sports Medicine exercise guidelines.[8] In line with the previous study, resting levels of myokines SPARC and OSM were significantly increased ($p < 0.05$) compared to controls, while no substantial differences were found in decorin, IGF-1, or IGFBP-3. When comparing the effects of serum on the prostate cancer cell DU145, cell growth was significantly decreased in the training group compared to controls (by 20%; $p < 0.05$). This underlines how chronic mixed-methods training with appropriate volume and intensity may alter resting myokine levels and can provide systemic and persistent changes which, in turn, create a less favorable environment for tumorigenesis; however, this finding was in contrast with that of Dethlefsen et al.[43] Additionally, and worth mentioning, despite the disease load and extensive and ongoing cancer treatments received by these patients, both acute and chronic training (as well as different training modes) showed positive effects on circulating blood factors and cancer cell suppression.

Cumulatively, the current literature on prostate cancer appears promising, with significant and clinically meaningful alterations of circulating factors and tumor suppressive effects. Regarding the acute bout of exercise, investigations examining HIIT and MICT from moderate to high intensity (i.e., 50%−65% VO_{2max}, 50%−90% P_{max}, 70%−85% HR_{max}) for 60 min resulted in suppressive effects on cancer cell growth and proliferation.[20,48,59,65] In short-term training (i.e., 11 days), a 30- to 60-min MICT at 70%−85% VO_{2max} at least 4 days a week reduced cancer cell growth and increased apoptosis, with systemic changes induced by long-term training (i.e., 10 years) having cancer suppressive effects.[18,21,66,67] Lastly, HIIT alone and RT coupled with HIIT or MICT showed inhibitory effects on cancer cell growth and proliferation in chronic interventions when performed at a moderate to high intensity (i.e., 6−12 RM, RPE > 3, 85%−95% VO_{2max}) for at least 9 weeks, 3 days a week.[45,46,59,69]

5. Colorectal cancer

Colorectal cancer is the third most diagnosed cancer and the third leading cause of cancer death.[70,71] To the best of our knowledge, very few preclinical studies have been conducted to date and even fewer involving human subjects.[72] Although the evidence is sparse, we have summarized the current literature pertaining to the effects of exercise-conditioned serum on colorectal cancer cells, which is crucial given the incidence and detrimental effects of this cancer.

5.1. Studies in subjects without colorectal cancer

Orange and colleagues[73] recruited 16 obese, sedentary males to undertake 60 min of moderate intensity interval training (MIIT) comprising 6 × 5-min bouts of cycling at 60% $HR_{reserve}$ (Table 1). Serum measured immediately after the single bout of exercise revealed a significant increase in IL-6 (+24.6%; $p < 0.05$) from pre to post, while no changes were found in IL-8, TNF-α, OSM, and SPARC. When exercise-conditioned serum was applied to LoVo cells (i.e., colorectal cancer cell lines) *in vitro*, proliferation was significantly reduced by 4.2% when compared to serum in the resting state ($p < 0.05$). Additionally, a significant decrease by 5.7% in cell proliferation was observed when examining the exercise-conditioned serum as opposed to serum acquired from the participants following a non-exercise control condition ($p < 0.05$). Thus, although only IL-6 was significantly altered, serum taken immediately after exercise reduced colon cancer cell proliferation. These findings are similar to those observed in other studies following acute exercise in people with and without cancer.[20,44,48,59] It should be noted that this is the first study using MIIT in which it appears to be a sufficient stimulus, possibly because the population was obese with a mean age of 60 years.

5.2. Studies in patients with colorectal cancer

Similarly, Devin et al.[44] examined both the effects of a single bout of exercise and short-term training in 10 overweight and obese male colorectal cancer survivors. The single bout of exercise (i.e., HIIT) was based on 4 × 4-min bouts of cycling at 85%−95% HR_{max}, with 3 min of active recovery (total work 38 min) (Table 3). Significant increases were observed in IL-6, IL-8, TNF-α, and insulin levels (by 44.8%, 24.7%, 15.2%, and 38.8%, respectively) in serum acquired immediately after the acute exercise session ($p < 0.05$), with circulating factors returning to baseline levels 2 h post exercise. When applying the exercise-conditioned serum *in vitro*, a significant reduction was found in cell number for the colon cancer cell lines CaCo-2 (effect size: −1.7 to −1.1; $p < 0.05$)

and LoVo (effect size: −1.2 to −0.8; $p < 0.05$), which is similar to the results of investigations in other cancer populations.[43,48,74] Thus, HIIT performed at high intensity (i.e., 85%−95% HR_{max}) altered circulating factors and cancer cells, emphasizing that intensity is likely to be a potential moderator in promoting those alterations.

The short-term training program repeated the same HIIT undertaken 3 times weekly over a 4-week period. When examining the serum obtained at rest, there was no significant change in levels of IL-6, IL-8, TNF-α, insulin, glucose, or IGF-1, or in the viability of the cell lines CaCo-2 and LoVo compared to baseline[44] (Table 4). These results are in line with those of previous findings, where lack of change in blood contents translates to no apparent suppressive effects on cancer cells.[43] Our assumption is that the exercise volume selected (i.e., 38 min, 3 sessions per week, for 4 weeks) was insufficient to drive substantial alterations in blood collected at rest, as previously mentioned.[43]

Cumulatively, there is insufficient evidence to draw meaningful conclusions about exercise mode, volume, and intensity for this type of cancer population. Preliminary evidence shows that acute MIIT and HIIT performed at approximately moderate to high intensity (i.e., 60% $HR_{reserve}$, 85%−95% HR_{max}) for at least 40 min resulted in a reduction in cell number and proliferation and alterations in circulating factors to a modest extent only[44,73] while a 4-week HIIT program performed 3 days per week (i.e., short-term) at 85%−95% HR_{max} did not elicit substantial modifications on serum content as well as cancer cell number.[44]

6. Lung cancer

Lung cancer is the leading cause of cancer death worldwide.[75] As a result, compelling actions are required to mitigate the burden. However, the cancer load and co-morbidities that accompany a diagnosis of lung cancer make it difficult for experimental studies to be undertaken in this patient group.[76] Although the number of preclinical studies in this cancer type is increasing,[32,35−37,77] to date only 1 study has been conducted in humans involving lung cancer cells.[47]

6.1. Studies in subjects without lung cancer

Kurgan et al.[47] recruited 23 male university students to perform a single 1-min high-intensity (i.e., 90% of maximum workload) bout on a stationary cycle ergometer followed by 1 min of active recovery, which was repeated 6 times (Table 1). As previously reported, in this study, IL-6, IL-1β, IL-1α, TNF-α significantly increased 5 min after the acute exercise session ($p < 0.05$) and returned to baseline after 1 h.[78] The exercise-conditioned serum collected after exercise at 5 min, 1 h, and 24 h resulted in a reduction of lung cancer A549 cell proliferation by 84%−91% and in survival rates by 21.5%−35.8% ($p < 0.05$). Similarly, lung cancer cell lines H460 and H1299 showed a decrease in survival rates ranging from 33.5%−41.9% when cells were cultured with post-exercise serum ($p < 0.05$).

Thus, a brief HIIT protocol at high intensity (i.e., $90\%_{max}$ workload) resulted in suppressive effects on lung cancer cell proliferation and survival rates, similar to those with and without cancer.[20,44,48,59,73] However, additional studies, particularly in lung cancer patients, are required for definitive conclusions to be drawn.

7. Directions for future research

Although preliminary, current studies in healthy, obese, and cancer patients and survivors indicate that acute training sessions adopting HIIT, MIIT, MICT, and mixed training (i.e., RT plus HIIT or MICT) at moderate-to-high intensity for at least 40 min confer an inhibitory effect on cancer cells and alter circulating factors.[20,42−44,47,48,59,73] In regard to short-term and chronic training interventions, HIIT and MICT (alone or coupled with RT performed for at least 30 min, 3 days a week) result in an alteration in resting circulating factors and provide a tumor suppressive effect.[18,21,22,43−46,59,66,67,69] However, future research is necessary to expand our understanding of the anti-cancer role of exercise (Fig. 1). The following are potential avenues of investigation:

(a) Further research should be focused on patients with cancer or a history of cancer (i.e., survivors) and, subsequently, stratifying by treatments (e.g., chemotherapy) or by disease stage. Furthermore, it should be noted that only studies in breast, prostate, colorectal, and lung cancer have been conducted to date, which represents a limitation of the current review and the state of knowledge more generally. The underlying reason is that cancer alters several physical and physiologic components.[79] Thus, studies conducted on healthy subjects showing modifications in circulating factors and cancer cell behaviors should be interpreted with caution, even though this was the logical first line of investigation. In support of this, it should be acknowledged that cancer treatments (e.g., ADT for patients with prostate cancer) or stages (e.g., localized prostate cancer *vs.* metastatic castrate resistance prostate cancer) may affect or impair a patient's ability to adapt with the morphological (e.g., muscle hypertrophy) and metabolic (e.g., hormonal adaptation) changes induced by exercise.[80] Thus, their responses may differ from those without cancer and, from a practical point of view, this may lead to more targeted and tailored training programs. In line with this, we may expand our knowledge about the timing of exercise in patients with cancer by exposing cancer cells to serum collected before, during, and after various cancer treatments *in vitro*. Furthermore, although it has not been discussed in detail, it was shown that elevated shear pressure caused by exercise in the circulatory system could induce apoptosis and necrosis of cancer cells in a dynamic-experimental setting using a microfluid system.[81] As such, evaluating the effects of shear stress induced by different exercise modes, volume and intensity on cancer cells in larger clinical trials would provide novel insight regarding targeted exercise prescriptions to reduce recurrence and metastasis of cancer.[81]

Fig. 1. Directions for future research for acute and chronic training interventions. Created with BioRender.com. AT = aerobic training; HIIT = high intensity interval training; MICT = moderate intensity continuous training; RM = repetition maximum; RT = resistance training.

(b) To deepen our knowledge of cancer suppressive mechanisms induced by exercise, it is necessary to design exercise trials with experimental models that include appropriate properties of cancer cell lines, co-culture systems, and parallel studies involving animal models and humans.[82] For instance, cancer cells in a co-culture system with cells known to promote cancer growth (e.g., adipocytes and immune cells) exposed to exercise-conditioned serum would provide biological insight about the impact of exercise on the interaction between cancer cells and cells around the tumor sites. Additionally, animal models could be employed to establish the *in vivo* causation of exercise-induced candidate factors, followed by validation in humans. Alternatively, the most optimal scenario for translating these findings to humans would involve window of opportunity trials.[83] Further, although it may be difficult to connect exercise mode, volume, and intensity in animal models and clinical trials, well-designed parallel animal and human studies will provide greater understanding of physical, physiological, and biological effects of exercise on specific cancer groups by validating preclinical outcomes in humans and *vice versa*.[82]

(c) In regard to training modes and chronic adaptations, most studies adopted a mixed mode approach incorporating both RT and AT.[43,45,46] This is likely due to the combination of training modes resulting in greater benefits over a wider range of outcomes for those with and without cancer (e.g., fat mass, lean mass, muscle strength, cardiorespiratory capacity, *etc*.). On the other hand, studies examining an acute exercise bout mainly used AT in the form of HIIT, MIIT, or MICT.[42,44,48,73] Although results are promising, investigations comparing different training modes (i.e., RT *vs.* AT), including also alternative RT training methods (e.g., cluster set training),[84] may elucidate whether different training stimuli result in different adaptations in both the acute and chronic training settings.

(d) The effects of acute exercise sessions appear to be primarily dictated by intensity.[20,42−44,48,59,65,73] In this case, blood taken immediately after a single bout of exercise has been shown to have a higher content of circulating factors. However, it is still unknown whether there is a threshold that drives modifications to occur. Furthermore, it remains unclear whether a person's training status (i.e., trained *vs.* untrained) may play a role in eliciting exercise-induced factors after a single exercise session. Future investigations should explore single bouts of exercise conducted at different training intensities and with training statuses to determine whether a minimal threshold exists for impacting cancer cells.

(e) For short-term and chronic interventions, current findings show that a high volume of combined resistance and aerobic exercise (i.e., >3 days a week) is necessary to alter circulating factors.[21,22,45−47,66,67,69,85] Future studies should take into account that 8−12 weeks of RT (2 sets of 8−15 repetitions performed at a moderate intensity at least 2 times per week) and AT (30−60 min performed at a moderate-to-vigorous intensity at least 3 times per week)[8] are necessary to drive physical adaptations and, subsequently, changes in resting circulating factors (e.g., myokines).[86] However, future investigations should explore what amount of training volume, frequency, and duration is required to induce such alterations. Additionally, whether more volume results in greater cancer suppressive effects is yet to be determined.

(f) In regard to circulating factors, future investigations should examine myokines in depth, owing to their potential direct tumor suppressive effects observed to date (Fig. 2).[87] In particular, determining whether or not

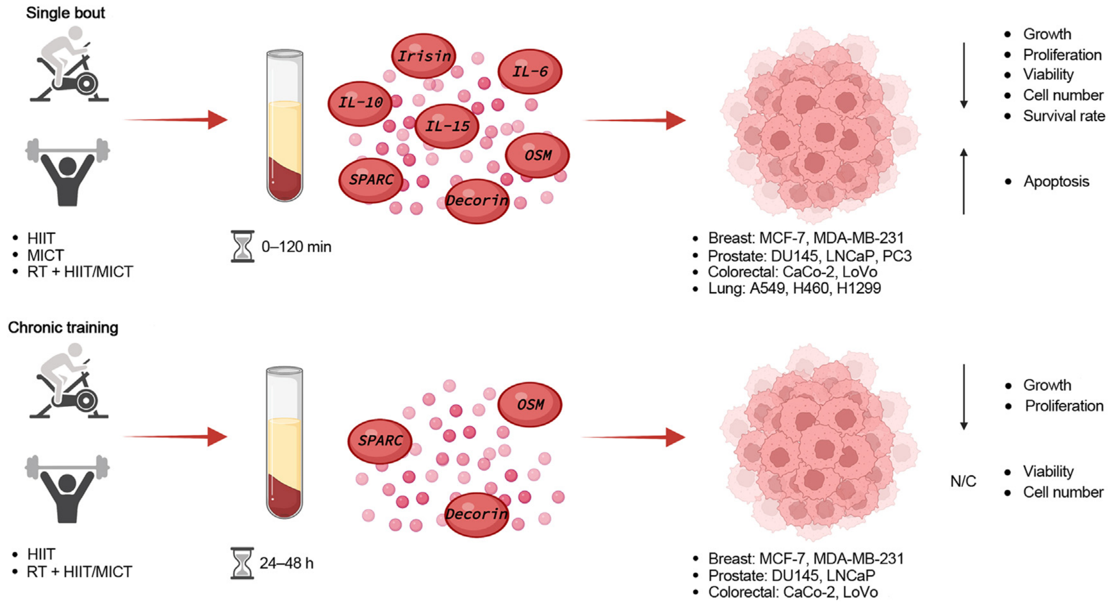

Fig. 2. Exercise-induced myokines in single bout and chronic training interventions and their effects on cancer cell lines. Created with BioRender.com. To be considered chronic, only training interventions >4 weeks have been included. ↑ = increase; ↓ = decrease. HIIT = high intensity interval training; IL = interleukin; MICT = moderate intensity continuous training; N/C = no changes; OSM = oncostatin M; RT = resistance training; SPARC = secreted protein rich in cysteine.

different training modes (i.e., RT *vs.* AT), volume and intensity elicit different responses in myokine expression in patients with cancer or survivors is of utmost importance to clearly elucidate potential underlying mechanisms and, therefore, implement practical applications in exercise oncology.[88]

(g) Lastly, it is unclear whether changes in body weight and body composition as a result of exercise training, disease, and treatments are related to different expressions of resting blood content. Our assumption is that an association may exist between body weight, body composition, and circulating factors (e.g., myokines). This comes from the fact that myokines are produced by skeletal muscles and a "higher" volume of this endocrine organ may translate to higher production;[89] however, this is only speculative. Thus, further research may explore to what extent alterations in body weight and body composition (in chronic interventions) relate to changes in circulating factors, and whether patients with higher skeletal muscle mass would have a higher myokine response after an acute bout of exercise.

8. Conclusion

The potential anti-cancer and tumor suppressive effects of exercise have garnered increased attention in the past 2 decades. Several avenues of research demonstrate that exercise-conditioned serum has inhibitory effects on cancer cell growth and promotes apoptosis in different cancer cell lines. However, the precise role played by different training modes, volume, and intensity on exercise-conditioned serum and its effects on cancer cells remains unclear. The limited number of studies available in a relatively new area of exercise oncology precludes definitive conclusions to be drawn. However, the findings to date show that a single moderate-to-vigorous intensity bout of AT may have suppressive effects on cancer cells and elicit substantial increases in circulating factors. When examining short-term and chronic training interventions, it appears that training volume may play a role in inhibiting cancer cells and altering circulating factors, regardless of the training mode used. Future research should be directed to targeted investigations into the effects of exercise-conditioned serum on cancer cells based on specific training modes (i.e., RT *vs.* AT), volume, and intensity, to better understand the underlying mechanisms to induce suppressive cancer effects and alterations in circulating factors while considering muscle and fat mass and changes in body composition due to disease and treatments as well as exercise medicine and diet therapy intervention.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

FB conceived the study design, searched studies in databases, elaborated the results, and drafted the manuscript; DRT, DAG, CB, JSK, and RUN edited and revised the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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