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Effects and potential mechanisms of exercise training on cancer progression: A translational perspective

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Abstract

Over the past decade there has been increasing research and clinical interest in the role of exercise therapy/rehabilitation as an adjunct therapy to improve symptom control and management following a cancer diagnosis. More recently, the field of 'exercise – oncology' has broadened in scope to investigate whether the benefits extend beyond symptom control to modulate cancer-specific outcomes (i.e., cancer progression and metastasis). Here we review the extant epidemiological evidence examining the association between exercise behavior, functional capacity/exercise capacity, and cancer-specific recurrence and mortality as well as all-cause mortality individuals following a cancer diagnosis. We also evaluate evidence from clinical studies investigating the effects of structured exercise on blood-based biomarkers associated with cancer progression/metastasis as well findings from preclinical investigations examining the effects and molecular mechanisms of exercise in mouse models of cancer. Current gaps in knowledge are also discussed.

Keywords

Exercise; Physical activity; Mouse models; Cancer; Carcinogenesis; Mechanisms

1. Introduction

The health benefits of regular exercise have been recognized for centuries. Indeed, structured exercise training is established as the cornerstone of primary and secondary disease prevention in multiple clinical settings. In contrast, it has not been until the past decade or so that exercise has gained acceptance as a potential adjunct therapy following a cancer diagnosis (Jones and Demark-Wahnefried, 2006; Jones et al., 2010a). To date, approximately, 80 studies have been conducted investigating the effects of structured exercise training in patients following a diagnosis of cancer. Meta-analyses and systematic reviews report that structured exercise training is a safe and well-tolerated therapeutic strategy associated with significant improvements in a broad range of cancer-related toxicities including fatigue, exercise capacity, and physical quality of life (Jones et al., 2011; McNeely et al., 2006; Speck et al., 2010). Based on the extant literature, several national and international organizations have published exercise guidelines for cancer patients both during and following the completion of adjuvant therapy (Hayes et al., 2009; Schmitz et al., 2010).

While the importance of exercise therapy to control and/or mitigate the adverse consequences of cancer therapy are undisputed, there is growing interest in determining

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whether the benefits extend beyond symptom control to modulate cancer-specific outcomes (i.e., cancer progression and metastasis). Elucidation of the effects and underlying mechanisms will be critical to inform hypothesis-driven clinical trials and ensure the optimal safety and efficacy of exercise in cancer control. Accordingly, over the past several years, exercise–oncology researchers from a wide variety of disciplines have started to investigate the association between exercise behavior, objective measures of exercise capacity/functional capacity, and prognosis following a cancer diagnosis as well as the cellular and molecular mechanisms underlying these associations. The purpose of this paper is to review: (1) the extant epidemiological evidence examining the association between exercise behavior, functional capacity/exercise capacity, and cancer-specific recurrence and mortality as well as all-cause mortality, and (2) studies elucidating the host and cellular mechanisms underlying the exercise–prognosis relationship. In terms of the latter, we evaluate evidence from clinical studies investigating the effects of structured exercise training ('structured' exercise is defined as studies testing a specific plan of physical activity designed to improve exercise capacity as opposed to studies designed to increase physical activity) on changes in blood-based biomarkers proposed to mediate the association between exercise behavior/exercise capacity and cancer-specific prognosis.

Further, we also review the evidence from preclinical investigations examining the effects of exercise on tumor progression and metastasis in mouse models of cancer.

2. Search strategy

A comprehensive literature review using PubMed, MEDLINE, Sport Discus, and Cochrane Controlled Trials Register (1966 through January, 2012) was conducted using the following MESH terms and text words: exercise, cardiorespiratory fitness, exercise capacity, cardiopulmonary fitness, functional capacity, oncology, and cancer. Relevant reference lists were also hand-searched. Studies in pediatric patients (<18 years) and adult patients with hematological malignancies were excluded.

3. Relationship between exercise and prognosis: epidemiological evidence

As summarized in Table 1 and 20 epidemiological studies to date have examined the association between self-reported exercise behavior and prognosis following a diagnosis of cancer. (Bertram et al., 2011; Borugian et al., 2004; Chen et al., 2011; Dal Maso et al., 2008; Holick et al., 2008; Holmes et al., 2005; Irwin et al., 2011, 2008b; Jones et al., 2011; Kenfield et al., 2011; Meyerhardt et al., 2006a, 2009a,b, 2006b; Moorman et al., 2011; Morikawa et al., 2011; Pierce et al., 2007; Richman et al., 2011; Ruden et al., 2011; Sternfeld et al., 2009). In brief, the majority of studies were conducted in women with early breast cancer (50%), with fewer conducted in patients with gastrointestinal malignancies (25%) and prostate cancer (10%). One study each was performed in patients with ovarian, non-small cell lung cancer, and primary malignant glioma. Overall, 15 studies (75%) found a significant inverse relationship between exercise and prognosis (cancer-specific or all-cause mortality) with a range of risk reduction between 15% to 67% and 18% to 67% for cancer-specific mortality and all-cause mortality, respectively. A dose–response was reported in 11 (55%); five studies found no significant association between exercise and cancer-specific mortality. Finally, the dose of exercise required for mortality reduction was not uniform either within or between cancer populations ranging from ≥9 metabolic equivalent time (MET)-hours per week of exercise (MET-h wk^{-1}) of moderate intensity exercise (equivalent to approximately 180 min wk^{-1} of moderate intensity exercise) to ≥27 MET-h wk^{-1} (equivalent to ≥500 min wk^{-1} of moderate intensity exercise).

Of importance, the association between exercise and cancer-specific mortality is not uniform and appears to vary according to volume of physical activity and even cancer type. For

example, the first reported study in women with early breast cancer found that that women reporting ≥9 MET-h wk^{-1} (equivalent to walking briskly for 30 min, 5 days/week), had a 6% reduction in unadjusted absolute mortality risk at 10 years compared with women who reported less than 3 MET-h wk^{-1} (equivalent to walking 2–2.9 mph for 1 h) (Holmes et al., 2005). In contrast, Holick et al. that found to ≥21 MET-h wk^{-1} (brisk walking for 75 min, 5 d wk^{-1}) was required for significant reductions in cancer specific and all-cause mortality in women with invasive breast cancer.

The majority of studies in women with early breast cancer have examined the association between exercise levels in the period following the completion of primary adjuvant therapy (i.e., surgery, radiotherapy, chemotherapy) and prognosis. Of interest, Borugian et al. found that self-reported exercise before adjuvant therapy was not associated with breast cancer mortality at 10 years. The reasons for the discrepant findings are not known but may relate to significant reductions in exercise behavior during primary adjuvant therapy (Irwin et al., 2003) or the lack of additional protective effect of exercise in combination with adjuvant therapy. To this end, exercise may be more effective as a 'secondary' adjuvant therapy. In other words, from a disease recurrence perspective, exercise may be more effective as a chronic maintenance adjunct therapy following the completion of primary adjuvant therapy akin to long-term endocrine therapy, although evidence to support this notion is currently lacking. The lack of uniformity of the association between exercise and prognosis following a breast cancer diagnosis also appears to translate to other solid malignancies. Specifically, in a series of studies by Meyerhardt and colleagues, they found that ≥18 MET-h wk^{-1} (equivalent to walking briskly for 60 min, 5 days/week) was associated with 36% to 40% reductions in colorectal-specific mortality and all-cause mortality in one study whereas ≥27 MET-h wk^{-1} (equivalent to walking briskly for 90 min, 5 days/week) was required to confer the equivalent reduction in colorectal-specific mortality and all-cause mortality in 668 patients with colorectal cancer.

The lack of consistent effects of exercise on cancer-specific outcomes may be partially explained by differences in tumor biology (phenotype) or expression of certain molecular markers. For example, Holmes et al. (2005) found that ≥9 MET-h wk^{-1} was associated with a relative risk reduction in mortality of only 9% in women with estrogen receptor (ER) negative tumors relative to a mortality reduction of 50% in women with ER positive tumors. This finding was corroborated by Irwin et al. (2008) In a detailed analysis of tumor samples obtained at the time of surgical resection, Meyerhardt et al. (2009c) found that patients with tumors exhibiting loss of p27, a protein that regulates cell cycle, the hazard ratio (HR) for colon cancer-specific mortality was 1.40 (95% CI, 0.41–4.72) for those reporting ≥18 MET-h wk^{-1} compared with <18 MET-h wk^{-1}. The corresponding HR for patients with tumors exhibiting expression of p27, was 0.33 (95% CI, 0.12–0.85) for those reporting ≥18 MET-h wk^{-1} compared with <18 MET-h wk^{-1}. In subsequent analyses Morikawa et al. found that patients reporting ≥18 MET-h wk^{-1} whose tumors did not express CTNNB1 (β-catenin), a key mediator of the WNT signaling pathway that plays an important role in colorectal carcinogenesis, had an adjusted HR for colorectal cancer-specific survival of 0.33 (95% CI: 0.13–0.81) compared with patients reporting <18 MET-h wk^{-1} (Morikawa et al., 2011). Conversely, there was no significant relationship between exercise and prognosis in patients with tumors that were positive for nuclear CTNNB1 (adjusted HR: 1.07; 95% CI: 0.50–2.30). Although more studies are clearly required, the putative evidence provides promising preliminary evidence that regular exercise may be protective in select types (i.e., histological or molecular sub-types) of solid malignancies.

4. Relationship between fitness and prognosis: epidemiological evidence

The vast majority of studies to date in the field of exercise–oncology have examined the relationship between self-reported exercise behavior (via surveys) and prognosis in cancer patients. While there are several advantages to self-report methodology, particularly in large observational epidemiological studies, these tools are subjective, lack sensitivity and have poor reliability and validity. In contrast, exercise tolerance tests provide an objective measure of exercise capacity or functional capacity. There are several methods available that provide an objective determination of exercise capacity. For a more detailed review of exercise testing methods in clinical oncology, the reader is referred to a prior review by our group (Jones et al., 2008).

The strong, independent prognostic importance of exercise capacity and functional capacity in numerous clinical populations is well-established (Warburton et al., 2006). However, a paucity of studies have examined the prognostic importance of these measures in patients with cancer. As summarized in Table 2, five studies to date have examined this question. In the first study, our group examined the prognostic value of peak oxygen consumption (VO_{2peak}), the gold standard assessment of exercise capacity. $VO_{2\text{-}peak}$ was a strong independent predictor of death in 398 surgical candidates with NSCLC after adjustment for KPS, age, gender, and pulmonary function (Jones et al., 2010c). In further work, we found that VO_{2peak} was also a strong predictor of all-cause mortality in 52 women with metastatic breast cancer. Again, VO_{2peak} added incremental value to the prediction of mortality beyond traditional markers of prognosis in this population (Jones et al.).

Three studies have also investigated the prognostic importance of measures of functional capacity, specifically 6-min walk distance (6MWD), in patients with cancer. Kasymjanova et al. investigated the association between 6MWD and survival in 64 patients with inoperable NSCLC (Kasymjanova et al., 2009). Relative to <400 m, a 6MWD ≥ 400 m was associated with a 56% reduction in the risk of death after adjustment for important covariates. In two subsequent studies by our group, we found that 6MWD was a strong, independent predictor of prognosis that provided incremental mortality risk prediction beyond traditional risk factors in patients with metastatic NSCLC, but was not associated with survival in patients with primary malignant recurrent glioma (Jones et al., 2011; Ruden et al., 2011). Of interest, in our metastatic NSCLC study, 6MWD remained an independent predictor of mortality after adjustment for self-reported exercise behavior, suggesting that an objective measure of exercise exposure (e.g., functional capacity) may provide a more sensitive prediction of mortality in patients with advanced cancer.

5. Mechanisms underlying the exercise-prognosis relationship

While the emerging literature base suggests that both self-reported exercise behavior and objective measures of exercise capacity/functional capacity are associated with survival in select cancer populations, the underlying biological mechanisms remain to be elucidated. Postulated mechanisms underlying the potential effects of exercise and/or fitness on cancer progression include modulation of metabolic (e.g., markers of glucose–insulin homeostasis) and sex-steroid (e.g., estrogens) hormone levels, improvements in immune surveillance, and reduced systemic inflammation and oxidative damage (McTiernan, 2008). However, to date, there is a paucity of correlative or direct evidence on these postulated host pathways in the clinical setting, or whether modulation of these pathways modulates the hallmarks of cancer in preclinical (animal) studies. Of course, there is a significant genetic contributor to exercise capacity therefore it is currently not clear how genetic predictors of exercise capacity relate to those contributing to cancer progression/metastasis or how the contribution of lifestyle factors (to exercise capacity) influence the fitness–prognosis relationship beyond

genetic contributions. These factors need to be considered when elucidating the mechanisms by which exercise and/or fitness may influence tumorgenesis. In the following sections, we review the available evidence from clinical studies investigating the effects of structured exercise on changes in blood-based biomarkers as well as data from preclinical investigations investigating tumor progression and metastasis in mouse models of cancer. Of note, unless otherwise stated, we assume that all blood-based measurements were performed in the resting state (and not immediately following an acute exercise bout).

5.1. Clinical data

As summarized in Table 3 and 24 studies to date have investigated the effects of structured exercise training on changes in circulating concentrations of host-related factors in persons with cancer (Allgayer et al., 2004, 2008a; Evans et al., 2009; Fairey et al., 2003, 2005a,b; Galvao et al., 2010; George et al., 2010; Irwin et al., 2006, 2007, 2005, 2009; Janelsins et al., 2011; Jones et al., 2012b; Ligibel et al., 2008; Na et al., 2000; Payne et al., 2008; Pierce et al., 2009; Schmitz et al., 2005; Segal et al., 2003, 2009; Tosti et al., 2011; Yuasa et al., 2009; Zeng et al., 2011).

The most widely investigated pathway is the effect of exercise on circulating metabolic factors, especially the insulin–glucose axis. Of the nine studies that evaluated these factors, most suggest that exercise is associated with changes in insulin-like growth factor-1 (IGF-1) concentration, insulin-like growth factor binding protein-3 (IGFBP-3) concentration, and IGF-1:IGFBP-3 M ratio, but there were no significant changes in insulin and glucose levels. Fairey et al. were the first to report that supervised exercise training following traditional exercise prescription guidelines (i.e., moderate intensity aerobic training at 60–75% of baseline VO_{2peak}, 3×/wk, 30–45 min/session for 15 weeks) was associated with significant alterations in IGF-1 concentrations (−7.4 ng/mL), IGFBP-3 concentrations (+180.5 ng/mL), and IGF-1:IGFBP-3 M ratio (−0.006) in 53 early-stage postmenopausal breast cancer patients compared to a sedentary control group (Fairey et al., 2003). There were no differences in fasting measures of glucose, insulin, or insulin resistance. Similar results were observed in larger studies of both aerobic and resistance exercise in breast cancer patients (Irwin et al., 2005; Janelsins et al., 2011; Schmitz et al., 2005). Ligibel et al. randomly assigned 101 overweight, sedentary early stage breast cancer patients to a 16-week home aerobic and resistance exercise program or sedentary control (Ligibel et al., 2008). Interestingly, in this population, patients experienced a borderline significant decrease in fasting insulin (28%, $p = 0.07$), a result that was corroborated by Irwin and colleagues (Irwin et al., 2009). Beyond breast cancer, Galvão et al. investigated the effects of a combined aerobic and resistance exercise training intervention metabolic factors in 57 prostate cancer patients undergoing androgen deprivation therapy. No significant differences were observed in any metabolic outcomes.

Exercise-induced effects on immune surveillance and inflammatory pathways have received some attention. Nine studies evaluated immunity and inflammation, but the results were quite variable. Na et al. reported that physical activity was associated with significant changes in *in vitro* function of natural killer cells isolated from gastric cancer patients (Na et al., 2000). Fairey et al. observed similar results as a result of 15-weeks of aerobic training in early stage breast cancer patients (Fairey et al., 2003). In this study, the authors also used ELISA to examine mononuclear cell cytokine production, but they did not see significant differences in either pro-inflammatory (e.g., IL-1, TNF-α, IL-6) or anti-inflammatory cytokines (e.g., IL-4, IL-10, transforming growth factor-1). A 2008 study by Payne et al. also reported no significant effects of exercise on serum IL-6 and cortisol levels in 20 postmenopausal breast cancer patients receiving hormonal therapy (Payne et al., 2008). In contrast, Allgayer et al. conducted a study of 23 stage II–III colorectal cancer patients after they completed primary therapy and found that short-term moderate intensity exercise was

associated with decreases in IL-1 receptor agonist response to stimulation with LPS in heparinized whole blood and a more pro-inflammatory state, which the authors defined as decreased ratios of IL-1ra/IL-6 and IL-1ra/IL-1β (Allgayer et al., 2004). One common measure of systemic inflammation is C-reactive protein (CRP), an acute-phase biomarker that has been widely shown to rise in the blood in accordance with systemic inflammation. Four studies, three in breast cancer and one in prostate cancer, have shown that exercise is associated with decreases in CRP levels (Fairey et al., 2005b; Galvao et al., 2010; George et al., 2010; Pierce et al., 2009).

Fewer studies have examined the effects of exercise training on markers of oxidative balance/status. Allgayer et al. found that short-term moderate intensity exercise significantly reduced urinary excretion of 8-oxo-dG, a marker of oxidative damage to DNA, in colorectal cancer patients after the completion of primary adjuvant therapy (Allgayer et al., 2008). In contrast, Jones et al. found that moderate to high-intensity cycle ergometry was associated with significant increases in F2-isoprostanes, eicosanoid markers of oxidative stress, in 16 patients with stage I–IIIB NSCLC (Jones et al., 2012b). Finally and somewhat surprisingly, a limited number of studies have examined the effects of exercise on circulating concentrations on sex-hormone factors –factors that are clearly of most relevance breast and prostate cancer. In terms of the latter, three studies to date have examined the effects of exercise on levels of testosterone in men with both early and locally-advanced prostate cancer; all studies to date have reported no change in testosterone or prostate-specific antigen between men randomized to exercise compared with sedentary control (Galvao et al., 2010; Segal et al., 2003, 2009).

Based on the current evidence, there are no clear conclusions regarding the efficacy of exercise training to modulate the postulated host-related mechanisms underlying the exercise–prognosis relationship. However, the postulated pathways appear reasonable targets since there is considerable evidence in healthy populations that exercise training can modulate circulating levels of metabolic hormones (Umpierre et al., 2011), immune/inflammatory factors (Walsh et al., 2011), and sex-steroid hormones (Friedenreich et al., 2010; McTiernan et al., 2004). Modulating effects of exercise on pro-oxidative and anti-oxidative products is less conclusive at present. Clearly, the pathways postulated to underpin the exercise–cancer prognosis relationship encompasses essentially all host-related factors in humans. As a consequence, there are literally hundreds of potential candidate biomarkers that could, in theory, modulate exercise efficacy. To tackle this issue, the integration of high-throughput discovery approaches in preclinical and/or clinical investigations will be critical to identify a parsimonious panel of exercise-responsive factors – the mechanistic action of which can then be further interrogated using an integrated approach involving *in vivo* and *in vitro* experiments. Following the identification of the major players within and across the various host-related pathways, the clinical importance of these factors can be examined in existing epidemiological datasets.

Whether exercise training can directly alter tumor biology in cancer patients has not been investigated. However, Yuasa et al. found an inverse association between self-reported exercise levels and methylation of CACNA2D3 in tumor tissue from 106 patients with gastric cancer (Yuasa et al., 2009). Similarly, Zeng et al. found a significant association between self-reported exercise levels and decreased methylation of the L3MBTL1 tumor suppressor gene in 75 postmenopausal women with stage 0–IIIA breast cancer (Zeng et al., 2011).

5.2. Preclinical data

The utilization of animal models is a critical scientific method to dissect the effects and underlying host-related and molecular mechanisms of exercise on tumor biology to

complement clinical investigations, to facilitate a translational approach to optimize the safety and efficacy of exercise in the oncology setting. Surprisingly, while numerous research groups have utilized mouse models to examine the effects of exercise on the initiation and incidence of several different cancer types (i.e., exercise exposure followed by tumor initiation), far fewer have adopted this experimental system to investigate the effects of exercise on progression and metastasis (i.e., initiation of exercise following tumor establishment, which mimics the clinical scenario of using exercise as an adjunct cancer therapy). As summarized in Table 4, we found a total of 14 studies investigating the effects of endurance exercise on a variety of different tumor types and endpoints, in several different model systems (Baracos, 1989; Cohen et al., 1991; Foley et al., 2004; Hoffman et al., 1962; Hoffman-Goetz et al., 1994b; Japel et al., 1992; Jones et al., 2005, 2010b; MacNeil and Hoffman-Goetz, 1993; Roebuck et al., 1990; Saez Mdel et al., 2007; Uhlenbruck and Order, 1991; Zheng et al., 2011; Zielinski et al., 2004). In summary, 11 (79%) studies reported primary tumor growth as an endpoint; of these, four found that exercise resulted in inhibition of primary tumor growth (Baracos, 1989; Cohen et al., 1991; Hoffman et al., 1962; Zheng et al., 2011). For example, Hoffman et al. implanted Walker 256 sarcoma cells subcutaneously into Wistar rats that were subsequently randomly allocated to voluntary wheel running in combination with daily swimming for 21 days relative to a sedentary control group. Tumor weight was significantly lower in the exercise group (percent of control: −97%) (Hoffman et al., 1962).

In contrast, three studies reported mixed results, meaning that tumor growth was inhibited in some exercise conditions and not in others (Roebuck et al., 1990; Uhlenbruck and Order, 1991; Zielinski et al., 2004).

Roebuck et al. examined the effects of up to 18 weeks of voluntary wheel running in a pancreatic adenocarcinoma model induced by injection of azaserine (Roebuck et al., 1990). They found that F344 rats that exercised had significantly fewer tumors and smaller volume percentage, but Lewis rats subjected to the same treatment did not exhibit significant differences between groups. In a different model, Uhlenbruck and Order injected L-1 sarcoma cells subcutaneously into BALB/c mice that were forced to run 200 m, 400 m, or 800 m daily on a treadmill (Uhlenbruck and Order, 1991). Tumor weight was significantly lower in the group that ran 200 m daily compared with sedentary animals, but there were no significant differences in tumor weight for the other distances. Additionally, Zielinski et al. injected EL-4 neoplastic lymphoid cells subcutaneously in BALB/c mice and found that forced treadmill running delayed tumor appearance, but there was no significant difference between groups with respect to maximum tumor volume (Roebuck et al., 1990; Zielinski et al., 2004).

Finally, in three studies tumor growth was comparable between exercise and sedentary control groups (Foley et al., 2004; Jones et al., 2005, 2010b). Foley et al. found no effect of 17 days of voluntary wheel running following subcutaneous injection of C10 sarcoma cells in F344 rats (Foley et al., 2004). Jones et al. observed similar results in two independent experiments in a model of human breast cancer. In the first, MDA-MB-231 breast cancer cells were subcutaneously into athymic nude mice and then randomized to 8 weeks of treadmill running or sedentary control (Jones et al., 2005). In the second experiment, MDA-MB-231 breast cancer cells were orthotopically implanted into the dorsal mammary fat pad and then animals were randomized to 41–48 days of voluntary wheel running or sedentary control (Jones et al., 2010b). In both experiments, exercise did not significantly inhibit or augment tumor growth. It is important to note that in contrast to the aforementioned studies, one has reported augmentation of primary tumor growth with exercise training. In this experiment, Sprague–Dawley rats were administered 7,12-dimethylbenz[α]anthracene to induce breast adenocarcinoma, and following tumor establishment, all animals were

randomized to forced swimming (30 min/day for 38–65 days) or sedentary control (Saez Mdel et al., 2007). Tumor growth rate increased 200% compared to control, although there were no significant differences in overall survival time.

The vast majority of cancer deaths result from metastasis, as such studies investigating the effects of exercise on metastatic dissemination and progression are of clear relevance. Only three studies to date have examined this question. In the first study, MacNeil and Hoffman-Goetz injected CIRAS1 transformed fibroblasts into the lateral tail vein of C3H/He mice and then randomized animals to voluntary wheel running or sedentary controls for three weeks (MacNeil and Hoffman-Goetz, 1993). Hoffman-Goetz et al. followed up on that work by injecting MMT 66 breast cancer cells intravenously into BALB/c mice and then randomizing animals to three weeks of treadmill running, voluntary wheel running, or sedentary control (MacNeil and Hoffman-Goetz, 1993). Exercise following tumor cell injection did not impact the development of lung metastases in either of these experiments. However, it is important to note that both of these experiments involved intravenous injection of cancer cells into otherwise healthy recipients, a model that fails to evaluate the ability of tumor cells to break through the tissue's basement membrane and invade into the capillary.

In an effort to address the limitations of prior research, our group examined the effects voluntary wheel exercise, compared with sedentary control, in male mice orthotopically implanted (into the prostate) with murine prostate cancer cells (TRAMP C-1). Results indicated that primary tumor growth rate was comparable between groups but expression of prometastatic genes was significantly modulated in exercising animals with a shift towards reduced metastasis (Jones et al., in press-a,2012a). Paradoxically, exercise was associated with significant increases in tumor vascularization, as measured by magnetic resonance blood perfusion imaging, while multiplex ELISAs revealed distinct reductions in plasma concentrations of interleukin-6 and CXCL1 in the exercise group. Based on the present data, we conclude that the effects of exercise on tumor progression and metastasis are equivocal. Reasons for the variable results to date likely pertain to differences in study methods, tumor cell line or carcinogen, location of tumor growth, and differences in the volume and type of exercise.

Researchers have also started to investigate the effects of exercise on host-related circulating factors as well as changes in the tumor phenotype that may mediate the exercise–tumor progression relationship. Specifically, three studies (21%) evaluated changes in intratumoral markers of neoplastic phenotype (Table 4). For example, in a model of azaserine-induced pancreatic cancer, Roebuck et al. reported that voluntary wheel running did not significantly affect the rate of DNA synthesis assessed by ^{3}H-thymidine incorporation (Roebuck et al., 1990). The other two experiments assessed markers of tumor angiogenesis. Zielinski et al. found that treadmill running decreased intratumoral blood vessel density in BALB/c mice subcutaneously with EL-4 neoplastic lymphoid cells (Zielinski et al., 2004). More recently, we found that voluntary wheel running increased hypoxia-inducible factor-1 protein levels and number of perfused blood vessels in athymic mice bearing human breast cancer xenografts, although there were no differences in protein levels of 5′ adenosine monophosphate-activated protein kinase, which regulates cellular energy homeostasis, or the angiogenic markers CD31 (a marker of endothelial cells) and vascular endothelial growth factor (Jones et al., 2010b). Two (14%) studies have examined changes in circulating concentrations of various growth factors with exercise, with both finding no changes in systemic glucose or prolactin levels (Cohen et al., 1991; Foley et al., 2004). Additionally, two studies investigated immune effects of exercise. Hoffman-Goetz et al. reported that lymphokine-activated killer cell activity was higher in exercising animals, whereas Japel et al. did not observe a difference in macrophage phagocytosis (Hoffman-Goetz et al., 1994a;

Japel et al., 1992). Overall, the effects of exercise on tumor growth and metastasis are inconclusive at present due to the low number and considerable heterogeneity between studies.

The existing literature base suggests that exercise may modulate select circulating concentrations of several different growth factors across multiple host pathways in both mouse and clinical studies. In conjunction, data from animal studies suggesting that exercise may impact tumor progression. Together, these data create a novel hypothesis that changes in these circulating factors in the host may, in turn, influence release of secondary factors from other organ sites such as the bone marrow, skeletal muscle, or liver with the end result of altering ligand availability in the primary tumor microenvironment and/or distant ectopic sites to influence tumorigenesis and metastasis, respectively. In other words, exercise may be a critical strategy to modulate the host–tumor interaction (Goodwin, 2008). The known effects and mechanisms of exercise on tumor progression adopting a bi-directional translational research approach is presented in Fig. 1.

Investigations that adopt a scientific discovery (also known as T0 or ‘bench-to-bedside’) translational approach are now required to elucidate to further understand the role and mechanisms of exercise to modulate host milieu–tumor–distant organ cross-talk. Such research will dramatically increase understanding of the mechanistic properties and application of exercise in the oncology setting.

6. Gaps in knowledge

Our recommendations for future research in this field are shown in Table 5.

7. Conclusion

There is growing recognition and acceptance of the beneficial role of exercise training/rehabilitation following a cancer diagnosis to prevent and/or mitigate disease and/or treatment-related toxicities to optimize symptom control and recovery. The results from an increasing number of epidemiological studies, however, suggest a previously unexpected role of exercise – as a therapeutic strategy to potentially delay cancer recurrence and mortality. It is important to stress that the evidence base is emergent with a small number of studies in comparison with the scientific literature base investigating the exercise–cancer prevention/incidence relationship. In addition, the strong association between exercise and prognosis following a cancer diagnosis are yet to be confirmed in randomized trials, although at least one trial is currently ongoing. For example, the Colon Health and Life-Long Exercise Change (CHALLENGE) trial is a phase III trial investigating the effects of regular exercise on recurrence and cancer-specific mortality in 962 colorectal cancer patients (Courneya et al., 2008). In conjunction with epidemiological studies and ongoing RCTs, a more thorough and structured understanding of the systemic and molecular mechanisms underlying the purported effects of exercise on tumor progression is critical. Such an understanding can be effectively achieved through the development of carefully designed correlative science (as part of forthcoming and/or ongoing randomized trials) or biomarker-driven studies together with a broad base of basic and clinical investigations encompassing a scientific discovery (T0 or ‘bench-to-bedside’) translational approach. This work will inform the design of adequately powered, mechanistically driven phase II–III trials to ensure that the appropriate exercise dose is prescribed to the right patients, at the right time, to facilitate the shift towards personalized, medicine to optimize therapeutic outcomes.

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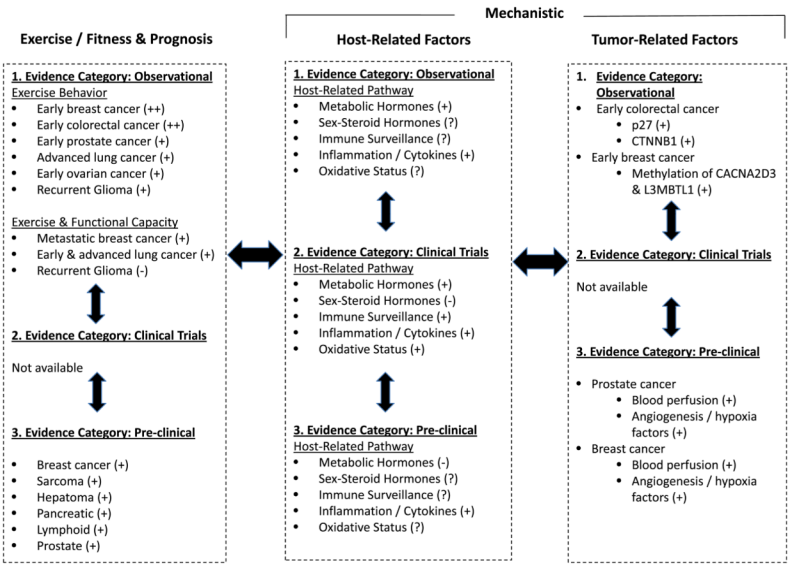

Fig 1.

Evidence-based representation of the known effects and mechanisms of exercise on tumor progression adopting a bi-directional translational research or scientific discovery (T0) paradigm. Exercise/fitness and prognosis, evidence supporting association between self-reported exercise behavior, objective measures of exercise capacity or functional capacity, and cancer prognosis; Host-Related Factors, postulated systemic (host-related) pathways mediating the association between exercise behavior and exercise/functional capacity and cancer prognosis; Tumor-Related Factors, intratumoral factors shown to mediate the association between exercise and prognosis or factors shown to be modulated in response to exercise. +++, strong evidence; ++, moderate evidence; +, weak evidence; —, null; ?, unknown at present.

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Table 1

Association between self-reported exercise and cancer-specific mortality and all-cause mortality.

Tumor type (study)	*N*	Cohort/setting	Cancer-specific mortality			All-cause mortality		
			Risk reduction	Physical activity dose	Dose response	Risk reduction	Physical activity dose	Dose response
Breast adenocarcinoma (Borugian et al., 2004)	603	Breast cancer patients after surgery before the start of adjuvant treatment	1.0 (multi-variate adjusted relative risk). Exercise was not associated with breast cancer mortality	>1 time/wk	No	n/a	n/a	n/a
(Holmes et al., 2005)	2987	Stage I–III breast cancer; Nurses' Health Study	0.5 (multi-variate adjusted relative risk)	9–14.9 MET-h/wk	No	0.56 (multi-variate adjusted relative risk)	15–23.9 MET-h/wk ($p < 0.05$)	No
(Pierce et al., 2007)	1490	Stage I–IIIa breast cancer; Women's Healthy Eating and Living Study	0.58	≥1320–6420 MET-min/wk	Yes	n/a	n/a	n/a
(Holick et al., 2008)	4482	Invasive breast cancer free of recurrence >2 years since diagnosis	0.51 (multi-variate adjusted relative risk)	≥21 MET-h/wk ($p < 0.05$)	Yes	0.44 (multi-variate adjusted relative risk)	≥21 MET-h/wk ($p < 0.05$)	Yes
(Irwin et al., 2008)	933	Breast cancer survivors; Health, Eating, Activity and Lifestyle Study	0.65 (multi-variate adjusted relative risk)	≥9 MET-h/wk	Yes	0.33 (multi-variate adjusted relative risk)	≥9 MET-h/wk ($p < 0.05$)	Yes
(Dal Maso et al., 2008)	1453	Invasive breast cancer survivors	0.85 (multi-variate adjusted relative risk)	≥2 h/wk	n/a	0.82 (multi-variate adjusted relative risk)	≥2 h/wk NS	n/a
(Sternfeld et al., 2009)	1970	Stage I–IIIa breast cancer; Life After Cancer Epidemiology	0.69 (multi-variate adjusted relative risk)	3 to <6 h/wk moderate activity	No	0.66 (multi-variate adjusted relative risk)	3 to <6 h/wk moderate activity ($p < 0.05$)	No
(Bertram et al., 2011)	2361	Stage I–III breast cancer survivors within 4 years, no current chemotherapy; WHEL study	n/a	n/a	n/a	0.47 (multi-variate adjusted relative risk)	≥24.7 MET-h/wk NS	Yes
(Chen et al., 2011)	4826	Stage I–III breast cancer, 6 mo after diagnosis; Shanghai Breast Cancer Survival Study	0.60 (multi-variate adjusted relative risk)	≥2 times/wk ($p < 0.05$)	Yes	0.70 (multi-variate adjusted relative risk)	≥2 times/wk ($p < 0.05$)	Yes
(Irwin et al., 2011)	4643	Invasive breast cancer survivors;	0.60 (multi-variate adjusted relative risk)	≥9 MET-h/wk ($p < 0.05$)	Yes	0.58 (multi-variate adjusted relative risk)	≥9 MET-h/wk ($p < 0.05$)	Yes

Tumor type (study)	*N*	Cohort/setting	Cancer-specific mortality			All-cause mortality		
			Risk reduction	Physical activity dose	Dose response	Risk reduction	Physical activity dose	Dose response
		Women's Health Initiative						
Colon/colorecta adenocarcinoma (Meyerhardt et al., 2006)	832	Patients with stage III colon cancer	0.51 (multi-variate adjusted relative risk), cancer recurrence or death from any cause (disease-free survival)	≥18 MET-h/wk ($p < 0.05$)	No	0.37 (multi-variate adjusted relative risk)	≥27 MET-h/wk ($p < 0.05$)	Yes
(Meyerhardt et al., 2006)	573	Women with stage I–III colorectal cancer; Nurses' Health Study	0.39 (multi-variate adjusted relative risk)	≥18 MET-h/wk ($p < 0.05$)	Yes	0.43 (multi-variate adjusted relative risk)	≥18 MET-h/wk ($p < 0.05$)	Yes
(Meyerhardt et al. 2009)	484	Men and women with colon cancer; Nurses' Health Study and Health Professional Follow-up Study	0.64 (multi-variate adjusted relative risk)	≥18 MET-h/wk ($p < 0.05$)	n/a	0.60 (multi-variate adjusted relative risk)	≥18 MET-h/wk ($p < 0.05$)	n/a
(Meyerhardt et al. 2009)	668	Men with stage I–III colorectal cancer; Nurses' Health Study	0.47 (multi-variate adjusted relative risk)	≥27 MET-h/wk ($p < 0.05$)	No	0.59 (multi-variate adjusted relative risk)	≥27 MET-h/wk ($p < 0.05$)	No
(Morikawa et al., 2011)	995	Men and women with stage I–IV colorectal cancer; Nurses' Health Study and Health Professionals Follow-up Study	In patients with negative CTNNB1 status and stages I–III cancer: 0.33 (multi-variate adjusted relative risk). No difference in survival for CTNNB1 + patients	≥18 MET-h/wk ($p = 0.05$)	Yes	n/a	n/a	n/a
Prostate adenocarcinoma (Kenfield et al., 2011)	2705	Men with prostate cancer from Health Professionals Follow-up Study	0.65 (multi-variate adjusted relative risk)	≥9 MET-h/wk ($p < 0.05$)	Yes	0.67 (multi-variate adjusted relative risk)	≥9 MET-h/wk ($p < 0.05$)	Yes
(Richman et al., 2011)	1455	Men with prostate cancer from CaPSURE Study	0.43 (for progression)	Walking ≥3 h/wk at ≥3 mph ($p < 0.05$)	No	n/a	n/a	n/a
Lung adenocarcinoma (Jones et al., 2012b, 2011)	118	Stage IIIb and IV NSCLC	n/a	n/a	n/a	0.67 (multi-variate adjusted relative risk)	≥9 MET-h/wk ($p < 0.05$)	n/a
Ovarian adenocarcinoma (Moorman et al., 2011)	638	Invasive disease; NC Ovarian Cancer Study	n/a	n/a	n/a	0.69 (multi-variate adjusted relative risk)	≥2 h/wk ($p < 0.05$)	No
Primary glioma (Ruden et al., 2011)	243	WHO grade III/IV recurrent glioma	n/a	n/a	n/a	0.64 (multi-variate adjusted relative risk)	≥9 MET-h/wk ($p < 0.05$)	Yes

Abbreviations: MET, metabolic equivalent task; NSCLC, non-small cell lung cancer; WHO, World Health Organization; NS, not-significant.

Table 2

Association between objective measures of cardiorespiratory fitness, functional capacity and all-cause mortality.

Tumor type (study)	*N*	Cohort/setting	Objective measure	Prognostic findings
Non-small cell lung cancer (Kasymjanova et al., 2009)	64	Newly diagnosed patients with stage IIIA, IIIB, or IV NSCLC with a life expectancy of at least 4 months	6MWT conducted three times: at time of enrollment, pre-chemotherapy, and after two cycles of chemotherapy	Patients with an initial 6 MWT ≥400 m had significantly longer survival than patients with initial 6 MWT < 400 m (multivariate adjusted HR: 0.44; 95% CI: 0.23–0.83; $p = 0.001$)
(Jones et al., 2010a,b,c)	398	Patients with suspected stage I–IIIA NSCLC who were candidates for primary surgery with an estimated life expectancy of at least 2 years; CALGB protocol 9238 Study	CPET on cycle ergometer to determine $VO_{2\ peak}$ measured once before surgery	Patients achieving $VO_{2\ peak}$ > 1.29 L/min had significantly better survival than patients with a $VO_{2\ peak}$ < 0.96 L/min (multivariate adjusted HR: 0.56; 95% CI: 0.39–0.80; $p = 0.0037$)
(Jones et al., 2010a,b,c)	118	Patients with histologically confirmed stage IIIB, IV or recurrent metastatic NSCLC	6MWT assessed one time	Patients achieving 6MWT ≥ 450 m had significantly better survival than patients with 6MWT <358.5 m (multivariate adjusted HR: 0.48; 95% CI: 0.24–0.93; $p = 0.025$). Every 50 m improvement in distance was associated with a 13% reduction in risk of death
Glioma (Ruden et al., 2011)	243	Patients with histologically confirmed WHO grades 3 and 4 malignant glioma who had received or were receiving salvage therapy	6MWT assessed one time	6MWT was not an independent prognostic factor. There was no significant difference in all-cause mortality between patients achieving 6MWT > 489 m and 6MWT <390 m (multivariate adjusted HR: 0.97; 95% CI: 0.63–1.48)
Breast adenocarcinoma (Jones et al., in press- a, 2012a)	52	Women with histologically confirmed IV breast cancer receiving cytotoxic chemotherapy	CPET on cycle ergometer to determine $VO_{2\ peak}$ measured once	CPET performance was not predictive of overall survival. Patients achieving VO_{2peak} ≥ 15.4 mL/kg-min did not have significantly different survival rates from those with a $VO_{2\ peak}$ ≤ 15.4 mL/kg-min (multivariate adjusted HR: 0.59; 95% CI: 0.29– 1.19; $p = 0.141$)

Abbreviations: 6MWT, 6 min walk test; CPET, cardiopulmonary exercise testing; NSCLC, non-small cell lung cancer; WHO, World Health Organization.

Table 3

Effects of exercise training on blood-based biomarkers from clinical studies.

Tumor type (study)	*N*	Design/cohort/setting	Biological mechanisms
Breast adenocarcinoma (Fairey et al., 2003)	53	RCT. Postmenopausal breast cancer patients randomized to a supervised 15-week aerobic training intervention or sedentary control	Exercise was associated with decreases in IGF-1 (10.9%, $p = 0.045$) and IGF-1:IGFBP-3 M ratio (18.2%, $p = 0.017$) and increase in IGFBP-3 ($p = 0.021$). No significant effect on fasting insulin, glucose, or insulin resistance
(Irwin et al., 2005)	710	Observational. Stage 0–IIIA breast cancer survivors; Health, Eating, Activity, and Lifestyle Study	Exercise was associated with significantly lower C-peptide ($p = 0.001$) and leptin levels ($p = 0.001$) and higher IGF-1 ($p = 0.0037$). There was a trend toward increased IGFBP-3 levels ($p = 0.055$)
(Fairey et al., 2005a,b)	53	RCT of exercise training in postmenopausal survivors of stage I–IIIB breast cancer who had completed surgery, RT, and/or chemo with or without tamoxifen or arimidex; Rehabilitation Exercise for Health after Breast Cancer Trial	Exercise was associated with a trend toward decreased C-reactive protein levels ($p = 0.066$)
(Fairey et al., 2005a,b)	53	RCT of exercise training in postmenopausal survivors of stage I–IIIB breast cancer after surgery, RT, and/or chemo with or without tamoxifen or arimidex; Rehabilitation Exercise for Health after Breast Cancer Trial	Exercise was associated with increases in natural killer cell cytotoxic activity ($p = 0.035$) and unstimulated mononuclear cell function ($p = 0.007$). No significant differences were observed in blood mononuclear cell production of pro-inflammatory (IL-1, TNF-α, IL-6) and anti-inflammatory cytokines (IL-4, IL-10, transforming growth factor-1)
(Schmitz et al., 2005)	85	RCT. Posttreated breast cancer patients 4–36 months after adjuvant therapy.	Six months of weight training significantly decreased IGF-II ($p = 0.02$) and IGFBP-3 levels ($p = 0.03$). There were no significant changes in glucose, insulin, IGF-I, IGFBP-1, and IGFBP-2
(Irwin et al., 2006)	474	Observational. Stage 0–IIIA breast cancer survivors; Health, Eating, Activity, and Lifestyle Study	Exercise was associated with a significant decrease in mammographic dense area ($p = 0.046$) and percent density ($p = 0.026$) in postmenopausal women with BMI ≥ 30 kg/m^2. Exercise was associated with a significant increase in percent density in premenopausal women with BMI < 30 kg/m^2 ($p = 0.037$)
(Irwin et al., 2007)	522	Observational. Stage 0–IIIA breast cancer survivors; Health, Eating, Activity, and Lifestyle Study	Exercise was associated with a significant decrease in mammographic dense area in postmenopausal women with BMI ≥ 30 kg/m^2 ($p = 0.036$). Exercise was associated with an increase in dense area in women with BMI < 25 kg/m^2, but this difference was not statistically significant
(Payne et al., 2008)	20	RCT. Postmenopausal breast cancer patients receiving hormonal therapy	No significant differences were observed between groups with respect to cortisol or IL-6 levels. Serotonin levels ($p = 0.009$) were significantly affected by exercise
(Ligibel et al., 2008)	101	RCT. Sedentary, overweight early stage breast cancer patients to home-based aerobic and resistance training program or sedentary control for 16 weeks	Exercise was associated with a 28% reduction in fasting insulin ($p = 0.03$) and a nonsignificant improvement in insulin sensitivity ($p = 0.09$)
(Pierce et al., 2009)	741	Observational. Stage 0–IIIA breast cancer survivors; Health, Eating, Activity, and Lifestyle Study	Exercise was associated with significantly lower concentrations of C-reactive protein ($p = 0.005$) and non-significant decreases in serum amyloid A concentrations ($p = 0.06$)
(Evans et al., 2009)	14	Pre-post. Posttreated breast cancer patients within 6 months of completion of all major cancer therapy and healthy controls matched for age and physical activity level; Get REAL & HEEL Breast Cancer Program	Breast cancer patients had significantly lower post-exercise blood lactate levels following high-intensity exercise (70% of VO_{2max}, $p < 0.0005$). There was no significant difference between patients and sedentary controls at low (40%) and moderate (60%) intensity
(Irwin et al., 2009)	75	RCT. Sedentary postmenopausal breast cancer survivors diagnosed 1–10 years prior with stage 0–IIIA breast cancer after adjuvant treatment at least 6 months before enrollment	Exercise was associated with a decrease in insulin ($p = 0.089$), IGF-I ($p = 0.026$), and IGFBP-3 ($p = 0.0006$) levels

Tumor type (study)	*N*	Design/cohort/setting	Biological mechanisms
(George et al., 2010)	746	Observational. Stage 0–IIIA breast cancer survivors; Health, Eating, Activity, and Lifestyle Study	Physical activity offset the negative effects of poor diet quality on C-reactive protein levels ($p = 0.03$) in breast cancer survivors
(Tosti et al., 2011)	14	Pre-post. Stage I–III invasive breast cancer within 6 months of completion of all major cancer treatments and no evidence of metastatic disease, matched to healthy controls	Patients with breast cancer had significantly lower blood lactate response to exercise ($p \leq 0.05$) across a variety of intensities. There was a trend toward more elevated glucose responses in women with cancer before and after exercise ($p < 0.08$)
(Janelsins et al., 2011)	21	RCT. Sedentary patients with stage 0–IIIb breast cancer after primary treatment 1–30 months prior to enrollment	Insulin levels did not rise in exercising patients compared to an increase in sedentary controls that received psychosocial therapy (significance not reported). IGF-1 decreased more in exercising patients than controls and IGFBP-3 increased in the exercising group (compared with a decrease in the control group), but neither of these changes was significant
(Zheng et al., 2011)	75	Pre-post/observational. Physically inactive postmenopausal women diagnosed with stage 0–IIIA breast cancer after completion of adjuvant treatment at least 6 months prior to enrollment.	Exercise was associated with a significant reduction in methylation of the L3MBTL1 tumor suppressor gene ($p = 2.9 \times 10^{-5}$)
Colon/colorectal adenocarcinoma (Allgayer et al., 2004)	23	RCT. Stage II or III colorectal cancer patients at least 4 weeks after completion of primary therapy (surgery and radiation and/or chemotherapy)	Short-term (2 weeks) of moderate intensity exercise was associated with decreased IL-1 receptor agonist response to LPS ($p < 0.05$) and a more pro-inflammatory state (decreased LPS antagonist/IL-1β, TNF-α, and IL-6 cytokine ratio; $p < 0.05$ for IL-6, all others non-significant)
(Allgayer et al., 2008)	48	RCT. Colorectal cancer patients after completion of primary therapy (surgery and radiation and/or chemotherapy)	Short-term (2 weeks) of moderate intensity exercise significantly decreased urinary 8-oxo-dG excretion levels ($p = 0.02$). High intensity exercise resulted in a non-significant increase in 8-oxo-dG levels ($p = 0.18$)
Prostate adenocarcinoma (Segal et al., 2003)	155	RCT. Men with a confirmed prostate cancer diagnosis scheduled to receive at least 3 months of androgen deprivation therapy after enrollment	Exercise did not significantly affect testosterone or PSA levels
(Segal et al., 2009)	121	RCT. Men with a confirmed prostate cancer diagnosis scheduled to receive radiation therapy with or without androgen deprivation therapy after enrollment	Neither resistance nor aerobic exercise significantly affected hemoglobin, testosterone, or PSA levels
(Galvao et al., 2010)	57	RCT. Men with confirmed prostate cancer at least 2 months of androgen deprivation therapy and were expected to undergo at least 6 more months of ADT with no evidence of disease	Exercise was associated with a significant decrease in C-reactive protein ($p = 0.008$). No significant differences were observed in testosterone, PSA, cholesterol, triglyceride, insulin, glucose, or homocysteine levels
Gastric adenocarcinoma (Na et al., 2000)	35	RCT. Stomach cancer patients after surgery	Exercise was associated with a significant sequential change in function *in vitro* of natural killer cells isolated from stomach cancer patients ($p < 0.05$)
(Yuasa et al., 2009)	106	Observational. Patients with primary gastric carcinoma	There was an association between physical activity and decreased methylation of CACNA2D3 (commonly methylated, poor prognostic factor in gastric cancer) ($p = 0.03$)
Lung adenocarcinoma (Jones et al., 2011,2012b)	16	Pre-post. Stage I–IIIB non-small cell lung cancer	Exercise was associated with an increase in urinary F2-isoprostanes (markers of oxidative stress) ($p = 0.08$)

Abbreviations: RCT, randomized controlled trial; 8-oxo-dG-8-Oxo-2′-deoxyguanosine; BMI, body mass index; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein-3; RT, radiation therapy; LPS, lipopolysaccharide; PSA, prostate-specific antigen.

Table 4

Effects of exercise on tumor progression and metastasis in mouse models.

Tumor type (study)	Rodent model	Animal strain	Method of tumor initiation	Effect of exercise on primary tumor growth (% of control)	Description of primary tumor growth	Description of mechanistic findings	
						Intratumoral	Systemic
Breast adenocarcinoma (Cohen et al., 1991)	Rat	F344	Tail vein injection of 37.5 mg/kg NMU[b]	Inhibition (NE)	Exercise significantly delayed tumor appearance and increased tumor latency. Tumor incidence was significantly lower in exercised animals compared with controls. There was no significant difference in tumor burden or mean tumor volume	Not evaluated	Exercise did not significantly affect prolactin levels
(Hoffman-Goetz et al., 1994a,b)	Mouse	BALB/c	Lateral tail vein injection of 1×10^4 MMT 66 cells	Not evaluated	This study evaluated pulmonary metastases from a tail vein injection of tumor cells. Exercise beginning after tumor injection did not significantly affect multiplicity of lung metastases	Not evaluated	Mice that began running on a voluntary wheel only after tumor injection had significantly higher LAK cell activity than those that had access to a voluntary running wheel before and after tumor injection
(Jones et al., 2005)	Mouse	Athymic nu/nu	Subcutaneous injection of 5×10^6 MDA-MB-231 cells	No change (NE)	There was no significant difference in tumor growth delay	Not evaluated	Not evaluated
(Saez Mdel et al., 2007)	Rat	Sprague– Dawley	Gastric intubation of DMBA.[c] 5 mg weekly for 4 w.	Augmentation (+200%)	The exercise group had a significantly higher tumor growth rate. There were no significant differences in survival time or tumor multiplicity	Not evaluated	Not evaluated
(Jones et al., 2010a,b,c)	Mouse	Athymic	Orthotopic (dorsal mammary fat pad) injection of 1×10^6 MDA-MB-231 cells	No change (+21%)	There was no significant difference in survival time based on tumor growth to 1500 mm^3	The exercised group had significantly more perfused vessels. HIF-1 protein levels were significantly higher in the viable tumor the exercised group. There were no significant differences in the levels	Not evaluated

Tumor type (study)	Rodent model	Animal strain	Method of tumor initiation	Effect of exercise on primary tumor growth (% of control)	Description of primary tumor growth	Description of mechanistic findings	
						Intratumoral	Systemic
						of CD31, VEGF, ATP, PGC-1α, or AMPK	
Sarcoma (Hoffman et al., 1962)	Rat	Wistar	Subcutaneous injection of 2 cc of Walker 256 cell suspension (concentration not specified)	Inhibition (− 97%)	Tumor weight was significantly lower in the exercise group	Not evaluated	Not evaluated
(Uhlenbruck and Order, 1991)	Mouse	BALB/c	Subcutaneous injection of 2.5×10^4 L^{-1} cells	Inconclusive (−44% to +86%)	The group that ran 200 m daily had significantly lower tumor weights, but the other running distances did not significantly affect tumor weight	Not evaluated	Not evaluated
(Foley et al., 2004)	Rat	F344	Subcutaneous injection of 1×10^7 C10 cells	No change (− 31%)	There was no significant difference in tumor weight as a result of exercise	Not evaluated	Exercise significantly increased insulin-stimulated glucose transport. No significant differences in blood glucose levels or lipid peroxidation in skeletal muscle based on exercise treatment
Hepatoma (Baracos, 1989)	Rat	Sprague– Dawley	Subcutaneous injection of 20 μL Morris hepatoma 777 finely chopped tumors	Inhibition (− 25%)	Tumor weight was significantly lower in the exercise groups. No significant differences in tumor weight between groups exercised for different durations	Not evaluated	Not evaluated
Pancreatic adenocarcinoma (Roebuck et al., 1990)	Rat	F344, Lewis	F344 rats received 3 doses of 30 mg/kg azaserine 4–5 d apart. Lewis rats received one dose of 30 mg/kg azaserine[a]	Inconclusive (−1% to −11%)	F344 rats that were exercised had significantly fewer foci and smaller volume percentage of foci, but there was no difference in focal diameter. No significant differences in Lewis rats	No significant difference in the amount of DNA synthesis based on treatment condition	Not evaluated
Transformed salivary gland cells (Japel et al., 1992)	Mouse	NMRI	Subcutaneous injection of 1.5×10^6 S-180 cells	Not evaluated	Not evaluated	Not evaluated	Moderate intensity physical exercise begun after injection of tumor cells did

Tumor type (study)	Rodent model	Animal strain	Method of tumor initiation	Effect of exercise on primary tumor growth (% of control)	Description of primary tumor growth	Description of mechanistic findings	
						Intratumoral	Systemic
							not significantly change macrophage phagocytosis
Transformed fibroblasts (MacNeil and Hoffman-Goetz, 1993)	Mouse	C3H/He	Lateral tail vein injection of 3×10^5 CIRAS1 cells	Not evaluated	This study evaluated pulmonary metastases from a tail vein injection of tumor cells. Exercise beginning after tumor injection did not alter lung tumor density relative to sedentary controls	Not evaluated	Not evaluated
Neoplastic lymphoid cells (Zielinski et al., 2004)	Mouse	BALB/c	Subcutaneous injection of 2×10^7 EL-4 cells	Inconclusive (+5%)	Exercise significantly delayed tumor appearance. There was no significant difference in peak tumor volume. Non-syngeneic tumors were rejected by the immune system of exercised mice	No significant difference in the fluid content of tumors. Significant reduction in vessel density in exercised animals on days 6, 8, 10, and 14 compared to controls	Not evaluated
Prostate adenocarcinoma (Zheng et al., 2011)	Mouse	SCID	Subcutaneous injection of 2.5×10^6 LNCaP cells. Tumors grew for 4–6 wk then animals were castrated to mimic androgen deprivation	Inhibition	Voluntary wheel running moderately inhibited androgen-independent tumor growth	Not evaluated	Not evaluated

[a] Azaserine is a glutamine analog carcinogen used to induce pancreatic cancer in preclinical models.

[b] *N*-Nitroso-*N*-methylurea (NMU) is an alkylating agent used to induce breast cancer.

[c] 7,12-Dimethylbenzanthracene (DMBA) is an aromatic hydrocarbon used to induce breast cancer.

Table 5

Future directions for exercise–oncology research on cancer progression.

Epidemiological studies

- A greater number of large-scale studies assessing both self-reported and/or objective measures of exercise exposure with long-term follow-up and adequate event rates.
- Delineate the association no how changes in exercise behavior, functional capacity/cardiorespiratory fitness measures are associated with clinical outcome across all solid tumors.
- More studies determining the differential association between exercise and prognosis as a function of tumor phenotype/gene expression.
- More studies determining the differential association between exercise and prognosis as a function of host-related circulating factors postulated to mediate the exercise–prognosis relationship.

Clinical biomarker intervention studies

- Delineate the differential effects of differences in exercise prescription dose (e.g., frequency, intensity, duration, modality) on changes in salient biomarkers in randomized trials.
- Determine effects of exercise across different tumor types across the cancer continuum (i.e., from diagnosis to palliation) to expand current efforts as well as extend to other solid tumors where exercise has not been rigorously evaluated.
- Elucidate the most salient biomarkers of interest that mediate the exercise–cancer prognosis relationship to develop a standardized ‘exercise–oncology’ biomarker panel that is reproducible and can be evaluated/compared across studies.
- Determine the effects of exercise on circulating biomarkers in conjunction with procurement of tumor tissue and/or imaging biomarkers whenever possible.

Preclinical studies

- Orthotopic implantation of syngeneic tumor cell lines or induction of orthotopic tumors via transgenic or chemical methods in immune competent animals to enable investigation of effects on primary tumor growth and metastasis.
- Elucidate the optimal exercise frequency, intensity, duration, and progression, as appropriate. Confirmation of ‘training’ effect via muscle fiber or mitochondrial function analysis.
- Determine effects on systemic mechanisms (metabolic and sex hormones, inflammation, immunity, and products of oxidation) in conjunction with examination of intratumoral/tumor microenvironmental molecular mechanisms (e.g., cell signaling pathways, angiogenesis, metabolism, migration).

Potential translational (cross-cutting/transdisciplinary) studies

- Elucidation of the optimal dose of exercise to inhibit tumor progression/metastasis in mouse models of solid tumors to guide the dose of exercise to be tested in phase II randomized trials.
- Elucidation of the effects of exercise on both circulating and intratumoral mechanisms associated with tumor growth in mouse models to guide systemic (plasma) biomarker testing in completed and ongoing clinical exercise trials in cancer patients. For further mechanistic investigations, plasma/serum from patients exposed to exercise vs. control conditions can be applied to human cancer cells in vitro to investigate effects on markers of the neoplastic phenotype.
- In epidemiological studies, identify genes or histological sub-types that may mediate the association between exercise and prognosis. Next, in preclinical studies, confirm mechanism of action by examining the effects of exercise in clinically relevant mouse models where the identified gene/pathway/histological sub-type is over-expressed or ablated. For clinical translational, plasma/serum from patients (with the identified histological sub-type or over expression of a specific pathway) exposed to exercise vs. control conditions can be applied to human cancer cells in vitro for further mechanistic studies.