Effects of Exercise on Cancer Treatment Efficacy: A Systematic Review of Preclinical and Clinical Studies

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ABSTRACT

We systematically reviewed and synthesized evidence on the impact of physical activity/exercise on cancer treatment efficacy. We included six preclinical and seven clinical studies. Exercise significantly enhanced the efficacy of chemotherapy and tamoxifen in seven of eight rodent models in either an additive, sensitizing, or synergistic manner. In clinical studies, preliminary evidence indicates that exercise during neoadjuvant, primary, and adjuvant treatment may enhance efficacy of cancer therapies; however, no clinical study was designed for this purpose. Here we discuss the biological mechanisms of exercise-associated enhancement of therapeutic efficacy and propose future research directions to definitively examine the effects of exercise on cancer treatment and patient outcomes.

Introduction

Postdiagnosis physical activity, defined as any bodily movement produced by skeletal muscles that requires energy expenditure, was associated with improved cancer-specific and overall survival in observational studies (1, 2). Exercise, defined as a specific type of physical activity that is planned, structured, and repeatedly done to improve or maintain physical fitness, has been proposed to improve cancer survival outcomes via three main clinical pathways: (i) direct effects on tumor growth and metastasis, (ii) improved treatment completion rates, and/or (iii) improved cancer treatment efficacy (Supplementary Fig. S1; ref. 3). In terms of direct effects, exercise has been shown to slow tumor growth and progression in preclinical studies (4, 5). Although the biological mechanisms underlying this relationship have not been confirmed, there is emerging evidence that exercise induces antineoplastic effects at both the systemic and intratumoral levels (5–7). In regards to improved treatment completion, clinical studies have shown that exercise improves some cancer treatment–related side effects (8), which may translate into improved cancer treatment completion rates (9).

The effects of exercise on cancer treatment efficacy, however, have received less attention. The potential interactions between exercise and cancer treatment efficacy are complex and may depend on whether or not exercise has direct effects on tumor growth and metastasis (3). The systemic (e.g., improved immune and metabolic function, reduced inflammation) and local (e.g., improved tumor vascularization, blood flow, and infiltration) effects of exercise may improve the efficacy of cancer treatments (5). Theoretically, exercise may improve cancer treatment efficacy in an additive, sensitizing, or synergistic fashion (**Table 1**; ref. 3). Moreover, these proposed effects may be impacted by the tumor site, the treatment regimen, and individual factors (3).

To our knowledge, no systematic review has synthesized and evaluated existing research on exercise and cancer treatment efficacy. The aim of this systematic review was to provide an overview of the current preclinical and clinical evidence of the impact of physical activity and exercise on cancer treatment efficacy outcomes. We also sought to highlight important knowledge gaps and provide key recommendations for future research on this critically important topic.

Materials and Methods

This systematic review was registered with PROSPERO *a priori* (CRD42020142954) and executed using the PRISMA statement guidelines. Two reviewers (ARM and LY) independently searched three electronic databases (MEDLINE, Embase, Scopus) for preclinical and clinical studies of exercise (or physical activity) that included a treatment efficacy outcome measure and were published between December 31, 1999, and August 4, 2019. No search limits were set for study design, study population, or the language of publication. The search syntax was limited to treatment efficacy, cancer treatment, and exercise terms (Supplementary Table S1) combined using an "AND" term. The systematic search was updated on February 10, 2021.

Study selection and inclusion criteria

Two reviewers (LY and ARM) each screened half of the titles and abstracts to remove obviously irrelevant articles, with these decisions being mutually verified. The remaining abstracts were assessed for inclusion by one reviewer (LY) and exclusions were checked by the other reviewer (ARM). The full text of all remaining studies was obtained and assessed independently for final inclusion by two reviewers (LY and ARM), with any discrepancies resolved by discussion.

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Table 1. Possible effects of exercise on cancer treatment efficacy.

			Cancer treatment efficacy (ES = 4)		
			Reduced (ES < 4)	**Unchanged (ES = 4)**	**Enhanced (ES > 4)**
Exercise direct effect	Negative	(ES = −4)	Subtractive (ES = 0–3) Antagonistic (ES < 0)	Neutralized (ES = 4)	Sensitizing (ES > 4)
	Neutral	(ES = 0)	Antagonistic (ES < 4)	Inert (ES = 4)	Sensitizing (ES > 4)
	Positive	(ES = 4)	Antagonistic (ES < 4)	Redundant (ES = 4)	Additive (ES = 5–8) Synergistic (ES > 8)

Abbreviation: ES, hypothetical effect size.
Adapted with permission from ref. 3.

Observational and experimental studies of physical activity (or exercise) with at least one "nonactive" comparison (or control group) reporting a measure of treatment efficacy were eligible for inclusion. Treatment efficacy endpoints were based on tumor assessment and included measures of tumor response in accordance with the RECISIT 1.1 criteria for solid tumors (10). We also included disease-free survival and overall survival as clinical endpoints, with overall survival considered the most important measure of cancer treatment benefit in clinical trials. For ease of interpretation, treatment efficacy endpoints were grouped according to tumor response outcomes and time-to-event outcomes. Exercise intervention trials that enrolled participants both on and off cancer treatment were included if treatment efficacy outcomes were reported separately for patients on treatment. We excluded cross-sectional studies, published protocols, studies reporting treatment efficacy outcomes in relation to exercise performed after the completion of cancer treatment, and studies reporting multimodal interventions where the isolated effects of exercise could not be determined.

Data extraction and data synthesis

For each included study, one reviewer extracted the data (EH), a second reviewer (LY) verified the extracted data and made a summary assessment of study validity, and a third reviewer (ARM) verified the assessment of validity. Any discrepancies were resolved by discussion. Data on the following factors were extracted for each study: endnote record number, name of the first author, year of publication, journal, country, study objective, study design, measures of exercise for observational studies, and content of the intervention for interventional studies; the procedures for defining, recruiting, and sampling from the intervention and control groups; the characteristics and sample size of the study population; the frequency and duration of follow-up; the definition and measures of treatment efficacy; results of any descriptive data and statistical tests reported; subgroup analyses, and any evidence relating to effects on other tumor-related outcomes. When studies reported results from the same experiment (11, 12), the outcome data from the earlier publication (12) were not included.

Strategy for data synthesis

Data extracted from preclinical and clinical studies were synthesized separately. We summarized clinical studies by cancer treatment setting. Where possible, we presented the absolute and relative differences between the exposed/intervention and nonexposed/control groups in a quantitative narrative synthesis. Given the heterogeneity of the tumor sites, treatment modalities, study designs, and outcome metrics, a meta-analysis was not performed.

Risk of bias (quality assessment)

The methodologic quality of the included clinical studies was assessed using the Risk of Bias 2 (RoB2) assessment tool, an update to the original Cochrane risk of bias tool (13). The RoB2 evaluates the following domains in randomized controlled trials: randomization process; deviations from the intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result. The RoB2 was used to assess both randomized and nonrandomized controlled trials in the present review for consistent evaluation. One reviewer (LY) assessed study quality, which was verified by another reviewer (ARM) and any discrepancies resolved in discussion with a third reviewer.

Results

A total of 18,112 articles were retrieved from the initial search, and 162 full texts were screened. An updated search conducted on February 10, 2021, retrieved one additional study (14) and one unpublished study conducted by coauthors (15) that met the inclusion criteria. Articles screened and reasons for exclusion are illustrated in Supplementary Fig. S2. Thirteen studies were included in this review.

Six preclinical studies utilized eight rodent models including: breast ($n = 3$), melanoma ($n = 2$), Ewing sarcoma ($n = 2$), and pancreatic ($n = 1$) cancers. Seven clinical studies were identified and included cancers of the breast ($n = 3$), colon and rectum ($n = 2$), lymphoma ($n = 1$), and mixed sites ($n = 1$). We summarized the study characteristics (Supplementary Table S2) and findings in absolute and relative measures (Supplementary Tables S3 and S4) for each included study.

Rodent models

All preclinical studies were full factorial designs investigating the effect of aerobic exercise (treadmill/wheel running) and concurrent cancer treatment on treatment efficacy with four study arms: (i) control, (ii) exercise alone, (iii) cancer treatment alone, and (iv) exercise + cancer treatment (sample size in each arm ranged from 5 to 21). All but one of the studies (16) investigated the effect of exercise on the efficacy of a single chemotherapeutic agent in breast, melanoma, pancreatic, and Ewing sarcoma cancer models. Khori and colleagues (16) examined the effect of exercise on tamoxifen efficacy in a breast cancer model. The effect of exercise on cancer treatment efficacy for each study is summarized in **Table 2**.

In 2005, Jones and colleagues (17) conducted the first animal model (triple-negative breast cancer, MDA-MB-231 grown in nude mice) of exercise and cancer treatment efficacy. Exercise alone improved 45-day survival [16%; 95% confidence interval (CI), 2%–31%]

Table 2. Summary of the effects of exercise on cancer treatment efficacy in rodent models.

		Cancer treatment efficacy		
		Reduced	**Unchanged**	**Enhanced**
Exercise direct effect	Negative	Subtractive Antagonistic	Neutralized	Sensitizing Sturgeon 2014 (melanoma; ref. 19) Schadler 2016 (melanoma; ref. 20)
	Neutral	Antagonistic	Inert	Sensitizing Schadler 2016 (pancreatic; ref. 20)
	Positive	Antagonistic Jones 2005 (breast; ref. 17)	Redundant	Additive Betof 2015 (breast; ref. 18) Khori 2015 (breast; ref. 16)
				Synergistic Morrell 2019 (A673 Ewing sarcoma; ref. 21) Morrell 2019 (TC71 Ewing sarcoma; ref. 21)

compared with control (0%). However, exercise + doxorubicin resulted in a lower 45-day survival (20%; 95% CI, 7%–33%) compared with doxorubicin alone (35%; 95% CI, 17%–54%), suggesting an antagonistic effect of exercise on chemotherapy efficacy. In later female breast cancer models, Betof and colleagues (ER^-, 4T1 grown in immunocompetent mice; ref. 18) and Khori and colleagues (ER^+, MC4-L2 grown in immunocompetent mice; ref. 16) found that exercise alone reduced tumor volume compared with control (Betof: ∼600 mm^3 vs. ∼800 mm^3; $P < 0.01$; Khori: 0.37 cm^3 vs. 1.43 cm^3; $P < 0.05$). In addition, exercise + treatment (Betof: cyclophosphamide; Khori: tamoxifen) enhanced the effect of treatment alone on reducing tumor volume (Betof: ∼500 mm^3 vs. ∼600 mm^3; $P < 0.01$; Khori: 0.25 cm^3 vs. ∼1.0 cm^3; $P < 0.05$) consistent with an additive effect.

In two melanoma models (B16F10 grown in immunocompetent mice), Sturgeon and colleagues (19) and Schadler and colleagues (20) found that exercise alone increased tumor volume compared with control (Sturgeon: ∼625 mm^3 vs. ∼450 mm^3; Schadler: 1208 mm^3 vs. 803 mm^3); moreover, exercise + doxorubicin resulted in a greater tumor volume reduction compared with doxorubicin alone (Sturgeon: ∼175 mm^3 vs. ∼350 mm^3; $P < 0.05$; Schadler: 365 mm^3 vs. 748 mm^3; $P < 0.05$), suggesting that exercise had a sensitizing effect on chemotherapy efficacy.

Schadler and colleagues (20) also reported that in a pancreatic mouse model (PDAC-4662 grown in immunocompetent mice), there was no effect (i.e., neutral) of exercise alone on tumor volume compared with control (711 mm^3 vs. 848 mm^3). Nevertheless, exercise + gemcitabine resulted in a greater tumor volume reduction compared with gemcitabine alone (169 mm^3 vs. 426 mm^3; $P < 0.05$) consistent with a sensitizing effect of exercise on chemotherapy efficacy.

In two separate Ewing sarcoma tumor models (A673 and TC71 grown in nude mice), Morrell and colleagues (21) reported that exercise alone reduced tumor volume compared with control (171 mm^3 vs. 962 mm^3 and 336 mm^3 vs. 1,109 mm^3). In addition, exercise + doxorubicin resulted in a greater tumor volume reduction compared with doxorubicin alone (51 mm^3 vs. 771 mm^3; $P = 0.02$ and 186 mm^3 vs. 673 mm^3; $P < 0.001$), demonstrating a synergistic effect of exercise on chemotherapy efficacy.

Clinical studies

Of the seven clinical studies (11, 14, 15, 22–25) included in this systematic review, five were two-arm randomized controlled trials (11, 15, 22–24), and two were pre-post single-arm studies that used nonrandomized comparison groups (14, 25). In all studies, treatment efficacy was a secondary or exploratory outcome and reported as objective response rate (i.e., tumor volume and pathologic response rate), disease- or progression-free survival (PFS), or overall survival (or mortality; **Table 3**). The effect of exercise on treatment efficacy is summarized in **Table 4** according to cancer treatment setting, type, and efficacy endpoint. The risk of bias was rated as "low" in four studies, as "some concerns" in one study, and as "high" in

Table 3. Exercise timing, cancer treatments, and efficacy outcomes.

		Treatment efficacy outcomes	
Exercise timing	**Cancer treatment**	**Tumor effects**	**Time to event**
Neoadjuvant or primary	Chemotherapy Radiotherapy Immunotherapy	Objective response rate Tumor size	Disease-free survival Event-free survival Overall survival
Adjuvant	Chemotherapy Radiotherapy Immunotherapy Hormone therapy	N.A.	Disease-free survival Event-free survival Overall survival
Inoperable metastatic	Chemotherapy Radiotherapy Immunotherapy Hormone therapy	Objective response rate Tumor size Number of tumors	Progression-free survival Overall survival

Table 4. Summary of the effects of exercise on cancer treatment efficacy in clinical studies.

Exercise timing	Cancer treatment	Treatment efficacy outcomes	
		Tumor effects	Time to event
Neoadjuvant	Chemotherapy	↔ Rao 2012 (breast; ref. 23)	
	Chemoradiation	↑ Morielli 2021 (rectal; ref. 15)	
Primary	Chemotherapy	↑ Courneya 2009 (lymphoma; ref. 22)	
Adjuvant	Chemotherapy		↑ Courneya 2014 (breast; ref. 24) ↔ Kirkham 2020 (breast; ref. 14)
Inoperable metastatic	Chemotherapy Radiotherapy		↔ Chiarotto 2017 (colorectal; ref. 25) ↑ Rief 2016 (mixed; ref. 11)

Note: ↑, cancer treatment efficacy enhanced by exercise; ↔, cancer treatment efficacy unchanged by exercise.

two studies (Supplementary Table S5) primarily due to the nonrandomized design in some of the included studies.

Neoadjuvant treatment

A small pilot randomized controlled study ($n = 10$; ref. 23) compared the effects of a supervised boot-camp intervention to usual care on tumor volume in women receiving neoadjuvant chemotherapy for locally advanced breast cancer. In the exercise group, tumor volume was 5.06 cm at baseline and 3.59 cm after intervention, whereas in the control group, the initial tumor volume was 4.88 cm and 3.16 cm at follow-up, suggesting no effect of exercise ($P = 0.76$) on chemotherapy efficacy.

One study conducted in rectal cancer patients compared a supervised high-intensity interval training program during chemoradiation followed by an unsupervised moderate-to-vigorous intensity aerobic exercise program after chemoradiation ($n = 18$) to usual care ($n = 18$; ref. 15). Pathologic response was complete/near complete in 56% of participants in the exercise group compared with 18% in the usual care group (95% CI, 4%–43%; $P = 0.02$). After adjusting for baseline clinical disease stage, the rate of complete/near complete pathologic response remained significantly higher in the exercise group (OR = 8.1; 95% CI, 1.5–44; $P = 0.016$).

Primary treatment

In the Healthy Exercise for Lymphoma Patients (HELP) trial, Courneya and colleagues (22) randomized 122 lymphoma survivors (44.3% receiving chemotherapy, 55.7% no treatment) to an exercise intervention ($n = 60$) or usual care ($n = 62$). The exercise intervention consisted of 12 weeks of three times weekly supervised, progressive, moderate-intensity aerobic exercise with high-intensity interval training incorporated from week 7 onward. Exploratory analyses found a numerically superior effect of exercise on the clinical complete response (46.4% exercise vs. 30.8% control; $P = 0.24$) in the 54 participants that were receiving chemotherapy (22).

Adjuvant treatment

Courneya and colleagues (24) conducted the Supervised Trial of Aerobic versus Resistance Training (START) in the adjuvant chemotherapy setting, which randomized 242 patients with stage I to III breast cancer starting adjuvant chemotherapy to one of three arms: three times weekly supervised moderate-intensity aerobic training ($n = 78$) or resistance training ($n = 82$), or usual care ($n = 82$) for the duration of chemotherapy (24). In an exploratory analysis, the two exercise groups were combined and compared with the usual care group during a median follow-up of 89 months. A numerically superior risk reduction was observed in the exercise group (disease-free survival: HR = 0.68; 95% CI, 0.37–1.24; recurrence-free interval: HR = 0.58; 95% CI, 0.30–1.11; distant disease-free survival: HR = 0.62; 95% CI, 0.32–1.19; overall survival: HR = 0.60; 95% CI, 0.27–1.33) in the unadjusted model. The effect of exercise on mortality risk reduction appeared to be stronger in women with HER2-positive tumors (HR = 0.21; 95% CI, 0.04–1.02) and those who had completed at least 85% of their planned chemotherapy (HR = 0.50; 95% CI, 0.25–1.01; ref. 24).

Kirkham and colleagues (14) conducted a pre-post single-arm intervention where patients with stage I to IIIA breast cancer receiving adjuvant chemotherapy treatment ($n = 73$) receiving a supervised, progressive, combined aerobic, and resistance exercise program three times weekly were compared with a historical control group ($n = 85$) matched for diagnoses, treatments, age, and body mass index. After treatment completion, supervised exercise sessions reduced to twice weekly for 10 weeks followed by once weekly for an additional 10 weeks. During a median follow-up of 70 months, the rate of disease progression [$n = 8$ (11%) exercise; $n = 9$ (11%) in historical control, $P = 0.974$] and overall mortality [$n = 5$ (7%) in exercise intervention; $n = 6$ (7%) in historical control, $P = 0.78$] were similar in both groups.

Inoperable metastatic

Rief and colleagues (11) randomized 60 patients with stable spinal bone metastasis of mixed cancer diagnoses receiving radiotherapy to either a supervised resistance training intervention group ($n = 30$) or a passive physical therapy control group ($n = 30$) to compare bone survival (time from the first diagnosis of bone metastases to death), PFS, and overall survival. The intervention consisted of isometric spinal muscle training on radiotherapy days for the duration of treatment (2 weeks). The physiotherapy control group received hot towel rolls with essential oils on their thorax (11). At 24 months, bone survival was 42% in the exercise group compared with 30% in the control group. Similar findings were observed for disease-free survival (24.3 months exercise vs. 20.5 months control; $P = 0.295$), and overall survival (80% exercise vs. 70% control at 12 months, and 63% exercise vs. 57% control at 24 months; $P = 0.688$).

Chiarotto and colleagues (25) conducted a pre-post, single-arm intervention of once-weekly combined aerobic and resistance exercise training during chemotherapy for metastatic cancers. Survival outcomes were only assessed and analyzed for colorectal cancer patients ($n = 9$ in exercise intervention, $n = 10$ nonrandomized control; ref. 25). At 8-year follow-up, 14 of 19 patients with colorectal cancer had died, with a median survival of 2.45 years (95% CI, 1.9–6.4), with no effect of the exercise program on overall survival (HR = 0.98; 95% CI, 0.32–2.97).

Key Findings

In this first systematic review of the effects of exercise on cancer treatment efficacy, six preclinical studies (eight models) and seven clinical studies were included. Single-agent chemotherapy was the most common treatment modality tested among animal models, with one model examining hormone therapy. Exercise appeared to reduce the efficacy of chemotherapy (i.e., an antagonistic effect) in the first model on the topic (17), but enhanced the efficacy of cancer treatments in all subsequent preclinical studies. Exercise demonstrated a simple additive effect in two models (i.e., an enhanced treatment effect consistent with the combined positive independent effects of treatment and exercise; refs. 16, 18), a sensitizing effect in three models (i.e., an enhanced treatment effect despite neutral or negative independent effects of exercise; refs. 19, 20), and a synergistic effect in two models (i.e., an enhanced treatment effect larger than the combined positive independent effects of treatment and exercise; ref. 21). Taken together, preclinical studies suggest that exercise may improve chemotherapy efficacy irrespective of a negative, neutral or positive direct effect of exercise on tumor growth.

In the included clinical studies, there was evidence that exercise may improve the objective response rate to neoadjuvant chemoradiation in patients with rectal cancer (15) and to primary chemotherapy in patients with lymphoma (22, 26). Moreover, randomized trials of exercise during adjuvant therapy showed a numerically superior effect on both disease-free survival and overall survival in patients with early breast cancer (24) and bone metastases (11). Although these clinical studies suggest that exercise may enhance the efficacy of cancer treatments, there are inherent limitations in their design that confound interpretation. In the trials reviewed here, it is not possible to distinguish additive effects of exercise from interaction effects as we do not know the independent effects of exercise on tumor behavior in these clinical settings. Nevertheless, if exercise improves treatment outcomes, it may not matter whether the effect is additive, sensitizing, or synergistic. From this perspective, better quality studies are needed showing that adding exercise to a cancer treatment improves the treatment outcome.

Biological Mechanisms

There are several biologically plausible mechanisms whereby exercise may enhance the efficacy of cancer treatments. For instance, exercise may enhance the efficacy of cancer treatments through favorable adaptations in tumor pathway signaling, hormones, metabolism, inflammation, and immunogenicity (6). In addition, hypoxia is one important factor that impedes the efficacy of cancer therapies including chemotherapy, radiotherapy, and immunotherapy (27). Preclinical prostate cancer models have demonstrated that repeated bouts of exercise improve tumor vascularization and blood perfusion (28, 29). Moreover, in two preclinical prostate cancer models (30, 31), tumor blood flow increased by ∼200% and subsequently reduced tumor hypoxia by ∼50% during an acute bout of exercise.

Notably, the proangiogenic nature of exercise may, in principle, fuel tumor growth in the absence of treatment (32); however, in combination with treatment, exercise may improve the delivery of anticancer therapies to the tumor through its effects on blood flow (33). Nevertheless, as illustrated in **Table 2**, the addition of exercise to cancer treatments may reduce treatment efficacy under some scenarios (17). Although the reduced treatment efficacy associated with exercise was not statistically significant in that study, this finding highlights the need for further preclinical studies to establish the safety of exercise (or safe timing of exercise) using direct measures of tumor physiology (i.e., tumor blood flow, tumor hypoxia, tumor vascularization, and blood perfusion) and/or treatment efficacy.

Moreover, future preclinical studies should expand to additional cancer sites and subtypes, particularly those with suboptimal treatment efficacy due to intrinsic or extrinsic biological factors that may be influenced by exercise. Future preclinical studies should also consider treatment modalities other than chemotherapy and radiotherapy, as recent animal tumor models have suggested that exercise could lead to a favorable immune environment and thus may improve the efficacy of immunotherapy (34–36). Preclinical studies are particularly important to examine the effects of exercise on treatment efficacy by incorporating measures of the aforementioned hypothesized mechanisms. In addition to the mechanisms outlined above, exercise may influence cancer treatment efficacy through its effects on drug pharmacokinetics, which are largely unknown (37). Nevertheless, exercise has the potential to influence drug absorption, distribution, metabolism, and excretion and should be investigated in future studies.

Implications and Future Directions

There are several gaps in evidence identified in this systematic review that deserve attention. First, there are very few studies on this topic in both preclinical and clinical settings. Second, few studies have been designed with the goal of improving treatment efficacy and none have been powered using cancer treatment efficacy as the primary endpoint. Therefore, assessment of cancer treatment efficacy was *post hoc* and exploratory in the majority of the reviewed studies. Third, the findings of the included trials are considerably heterogeneous, with mixed cancer sites and stage, the timing of the intervention relative to treatment, and treatment regimens. Finally, very few studies included radiotherapy, immunotherapy, or other more recently developed anticancer therapies, which may also interact with exercise. Despite the inherent limitations of the reviewed studies, the evidence presented here is promising. In the past four decades, over 700 exercise trials in the oncology setting have been conducted to establish evidence for safety and feasibility, and whether exercise can improve physical function and quality of life outcomes among cancer survivors. Clinical studies with treatment efficacy as the primary outcome have been far fewer, probably because of the necessity of larger sample sizes, longer follow-up, and limited funding opportunities. Nevertheless, treatment efficacy is the most critical issue for cancer patient, and we need to develop novel methods and funding opportunities to make these trials happen. Therefore, trials designed to test the effects of exercise on cancer treatment efficacy endpoints are warranted.

Existing and future cohort studies that collect physical activity information before or during cancer treatment should consider the feasibility of data linkage in their design to examine the associations between physical activity and cancer treatment outcomes including objective response rates and survival outcomes. These studies may also begin to examine the biological mechanisms underlying the relationship between physical activity and cancer treatment efficacy by including biological samples (i.e., markers of angiogenesis, immune function, inflammation, metabolism). Alternatively, ongoing efficacy trials of new cancer treatments may collect physical activity information to examine their influence on treatment efficacy outcomes. An important consideration in

observational studies is to evaluate the specific tumor types (e.g., breast cancer hormone receptor status) that are sensitive to exercise to inform targeted interventions.

The design of intervention trials during cancer treatment will depend on cancer type, treatment type and timing, and individual factors. Specifically, in clinical settings where the goal is to shrink the tumor (e.g., neoadjuvant and metastatic settings, primary radiation for prostate cancer, primary chemotherapy for lymphoma) tumor response may be evaluated using a measure of objective response. Moreover, these trials should consider incorporating assessments of the mechanisms hypothesized to improve the effectiveness of cancer treatments. To reduce participant burden and increase recruitment, parallel trials of both human and rodent models are desired to capture treatment efficacy measures in the clinical setting and supplement biological mechanistic investigation in the preclinical setting. In clinical settings where the goal is to eradicate any residual tumor cells (i.e., adjuvant treatment), time-to-event outcomes with longer follow-up will be needed. Moreover, large sample sizes will be required to evaluate these outcomes and results may be confounded if exercise crossover is offered after treatment.

There may be clinical settings where a full factorial exercise and cancer treatment efficacy trial may be feasible. Such a setting would require a new cancer treatment being compared with a placebo (or no treatment). One example is the active surveillance setting, which is growing in popularity for patients with prostate cancer and being considered for other patients with cancer. In this setting, new treatments are being considered, and it may be possible to randomize patients to exercise in addition to the new cancer treatment, resulting in a full factorial human trial of exercise and cancer treatment efficacy. Similarly, patients with metastatic diseases might also be candidates for a full factorial exercise and cancer treatment efficacy trial if a new treatment is being compared with a placebo. If such trials are possible, it would allow for a full test of exercise and cancer treatment main effects and interactions, similar to the rodent studies. Such studies would provide the most definitive evidence on the complex effects of exercise on cancer treatment efficacy.

Conclusions

Altogether, the findings from the included studies suggest a potential positive effect of exercise on cancer treatment efficacy. To date, no clinical study has employed treatment efficacy as the primary endpoint or been designed to disentangle the direct effects of exercise on cancer progression from the interaction effect of exercise with cancer treatments. Several proposed biological pathways support a combined positive effect of exercise and cancer treatment. Future exercise oncology research designed to focus on treatment outcomes is needed to fully establish the safety and efficacy of exercise as a standard treatment for cancer.

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Authors' Disclosures

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