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Development of Exercise as Interception Therapy for Cancer: Learning from Lessons of the Past

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Abstract

Importance: Observational data linking physical activity and exercise exposure with either reduced risk or progression of cancer has fueled interest in the initiation of large-scale definitive trials to test the effects of exercise therapy on disease outcomes. However, several major knowledge gaps impede the rational and optimal design of such trials.

Observations: Critical prerequisites underpinning the success of several recent contemporary anticancer agents have included adequate demonstration of antitumor activity (in phase 1/2 trials) as well as identification of essential prerequisites (e.g., biologically effective dose, predictors of response) permitting optimal design of definitive trials. The existing evidence base investigating exercise as a candidate anticancer preventive or treatment strategy is predominantly confined to observational data – data with several inherent limitations. Consequently, the antitumor activity of exercise remains unclear and perhaps more importantly, such data is not sufficient to accurately derive the dose, prescription regimen, or patients most likely to benefit from exercise. In adherence with translational frameworks for lifestyle therapy development, we highlight the urgent need for early phase 1/2-equivalent trials to fill current knowledge gaps to optimize the development and potential efficacy of exercise therapy.

Conclusions and Relevance: Exercise therapy has significant promise to be a highly efficacious, low-toxicity, and cost-effective therapy to improve cancer outcomes. However, the majority of non-traditional therapies in cancer prevention and prognosis fail in definitive trials. We contend these failures provide critical lessons for the continued development of exercise as a candidate anticancer therapy.

Keywords

Exercise-oncology; physical activity; cancer drug development

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Introduction

Despite a considerable body of observational evidence and guidelines from multiple international agencies,[1–3] the prescription of exercise therapy is not considered standard of care for individuals at risk or with cancer. This scenario is in sharp contrast to the majority of other common chronic conditions wherein exercise therapy is considered 'first-line' primary or secondary preventive treatment. A reasonable explanation for the discrepancy in utilization of exercise therapy in oncology compared with other disease conditions likely relates to the fact that cancer is not a qualifying diagnosis for third party reimbursement of formalized exercise rehabilitation. In turn, the lack of reimbursement likely reflects the smaller body of evidence (in oncology), particularly data from definitive randomized controlled trials (RCTs) demonstrating improvement in "hard" outcomes or established surrogate markers of disease risk, progression or competing causes of mortality.[4] To this end, at least two large, international phase 3 RCTs are underway investigating the efficacy of exercise therapy on cancer outcomes in stage II–III colon cancer[5] and metastatic prostate cancer.[6] Several additional phase 3 RCTs evaluating the efficacy of lifestyle approaches (combination of diet and physical activity promotion) on disease outcomes in various cancer populations.[7,8]

From the perspective of therapeutic development, the launch of phase 3 trials of exercise therapy raises the critically important question of whether the current evidence base is sufficient to support the initiation as well as rational design of such trials. The development of contemporary targeted anticancer agents closely adheres to a well-established framework involving compound screening and preclinical testing followed by 'first in human' phase 0 trials, phase 1 / 2 trials, and ultimately phase 3 RCTs. Among the many advantages, particular strengths of such a standardized approach include: (1) the development of only those agents exhibiting biological / antitumor activity with acceptable safety profile, and (2) elucidation of key prerequisites permitting optimal design of definitive trials (when appropriate), including drug mechanism of action, optimal dose (and schedule), and predictors of response. A comparable mandated approach is not required for the development and testing of non-regulated candidate strategies including lifestyle interventions. Consequently, over the past two decades, numerous non-regulated therapies (e.g., vitamin supplementation,[9–11] metformin,[12,13] aspirin,[14] omega-3,[15] dietary modification,[16,17] psychosocial counseling[18]) have proceeded to definitive testing in cancer prevention or prognosis without having to achieve comparable developmental "go / no-go" milestones as that mandated in drug development.

It could be argued that a similar drug development-type framework is not required for non-regulated strategies for multiple reasons including (typical) stark differences in safety profile. However, the harsh reality is the vast majority of definitive trials of non-regulated therapies have either been negative or, in some instances, increased cancer incidence or other serious toxicities.[10,11,15,19] Indeed, two recent multi-center phase 3 RCTs, both including exercise as an intervention component, did not confer a disease-free or overall survival benefit in early breast cancer[20] or patients undergoing hematopoietic cell transplantation,[21] respectively. We contend major contributing factors to the general failure of these trials may relate to the lack of adherence to a standardized rigorous development framework, resulting

in therapies being advanced to definitive testing without: (1) adequate demonstration of antitumor activity (in smaller trials), and (2) identification of essential prerequisites (e.g., biologically effective dose, schedule) which permit rational or optimal trial design.

We recently proposed a translational framework specifically designed to facilitate investigation of exercise as a candidate anticancer strategy from initial epidemiology discovery to definitive RCTs.[4] In this Opinion article, we leverage the tenets of this framework to critically evaluate the evidence base in exercise-oncology pertaining to (1) antitumor activity, (2) the most appropriate dose (and schedule), and (3) identification of patients most likely to benefit from exercise. In the final section, we consider next steps in the continued development of exercise as anticancer therapy.

Antitumor Activity of Physical Activity and Exercise: Current Evidence

Physical activity is defined by the World Health Organization as any bodily movement produced by skeletal muscles that requires energy expenditure, whereas exercise is defined as a subcategory of physical activity consisting of planned, structured, repetitive, and purposeful. The vast majority of observational studies assess physical activity rather than exercise. On the basis of multiple meta-analyses[22–24] and pooled analysis,[25] the Physical Activity Guidelines Advisory Committee (PAGAC) determined strong evidence exists to support the conclusion that physical activity lowers the risk of colon, breast, kidney, endometrial, bladder, esophagus (adenocarcinoma), and stomach (cardia) cancers, with moderate evidence for lung cancer risk reduction.[26] The committee determined there was no relationship between physical activity and risk of thyroid or rectal cancers.[26] These conclusions are largely mirrored by others organizations.[27,28] In the post-diagnosis setting, the PAGAC concluded that moderate evidence supports associations among higher amounts of physical activity and lower risks of breast-, colon-, and prostate-specific mortality, as well as all-cause mortality.[26]

Observational data, of course, cannot prove causality. Preclinical testing is a major facet of drug development and can also be utilized to confirm the biological plausibility that exercise has anticancer activity. Unfortunately, preclinical testing of the antitumor activity of exercise is limited. A recent systematic review only identified a total of 53 *in vivo* preclinical studies evaluating the activity of various exercise paradigms on tumor incidence, growth, or metastasis; 35 of 53 studies reported exercise inhibited cancer growth or progression.[29] This evidence base, however, has considerable methodological weaknesses as well as heterogeneity in all aspects of study design, endpoints, and efficacy, precluding meaningful comparisons and conclusions regarding the preclinical activity of exercise in any cancer model. More recently, higher quality studies have demonstrated paradigms of physical activity[30] and exercise[31] have antitumor activity in several, but not all, mouse models of cancer. In drug development, positive preclinical data not only provides the basis to proceed with initial clinical testing but also informs starting dose as well as other study aspects. While data from definitive trials of exercise therapy on disease outcomes in either the prevention or post-diagnosis setting are not yet available at present, multiple RCTs have investigated whether exercise alters a wide-array of biomarkers postulated to underpin the exercise – cancer pathogenesis relationship (e.g., alterations in the circulating concentrations

of metabolic, sex-steroid growth factors and hormones, inflammatory cytokines, and DNA damage response / repair factors, breast mammographic density). Overall, exercise therapy of various doses (e.g., 150 mins, 300 mins/wk) and exposure periods (e.g., 6 to 12 months) are associated with small to modest alterations in a select number of markers, however effects across trials are inconsistent.[32,33] Moreover, whether the observed alterations have biological or clinical importance is uncertain.[34] Only one trial has investigated the effects of exercise on a biomarker (i.e., breast tissue density[35]), demonstrated as a strong predictor of breast cancer risk, but effects were negative.[36]

Hence investigation of whether exercise directly alters the evolution or biology of tumor / normal cells or the tissue / tumor microenvironment (TME) would be of immense importance to further the contention that exercise has biological antitumor activity.[37] A paucity of data is currently available however. In the prevention setting, moderate-to-vigorous intensity exercise therapy (planned dose ~360 mins/wk) for 12 months increased expression of the pro-apoptotic protein (Bax) in the bottom of the colon crypts among men, whereas it decreased among women in the middle of crypts.[38] In a preoperative 'window of opportunity' phase 2 RCT, 4 weeks of home-based exercise was associated with alterations in intratumoral gene expression, predominantly involving immune pathways, with no changes in tumor cell proliferation (Ki67) in 49 patients with primary breast cancer.[39] Finally, exploratory secondary analyses from at least two phase 2 RCTs suggest structured exercise therapy after diagnosis of primary breast cancer[40] or lymphoma[41] may favorably impact disease outcomes. However, caution is required when interpreting these data given neither trial was primarily designed nor powered to examine cancer outcomes.

In summary, the existing evidence base supporting the antitumor activity of exercise is confined predominantly to observational data – studies that use self-reported methods to measure physical activity or exercise exposure, with (very) limited confirmatory data from preclinical or clinical studies. The limitations of observational studies are well-established and include inaccurate assessment and quantification of physical activity, with high-risk of reverse causality.[42] In the next sections, we evaluate the evidence informing the most appropriate dose (and schedule) as well as predictors of response – essential requisites for optimal design of definitive trials.

Exercise Treatment Regimen

Dose:

Arguably, the most critical consideration in the design of definitive RCTs testing any medical intervention is the treatment regimen (prescription). As described, the majority of evidence supporting antitumor activity of physical activity and exercise is from observational studies. Table 1 provides a brief overview of physical activity measurement and quantification methodology used in most observational studies. In theory, therapeutic 'dose' level could be extracted from physical activity or exercise exposure associated with disease benefit within the cancer histology of interest, to guide dose and schedule for subsequent clinical trial evaluation. This approach, however, has major caveats.

First, the assessment and quantification of physical activity or exercise using self-report methods is imprecise.[42] For example, the energy expenditure (or metabolic cost) associated with the same activity (of the same duration) varies considerably due to inter-individual differences in both resting and maximal metabolic rate. Relatedly, the survey instruments vary across individual studies and are often inconsistent with absolute measurements (e.g., accelerometer) – thus, the definition as well as calculation of dose is neither uniform nor acurate.[43,44] Second, the amount of physical activity or exercise associated with reductions in either the primary risk or post-diagnosis disease outcomes varies considerably across individual studies. For instance, in studies examining breast cancer risk, the amount of physical activity or exercise associated with significant reductions range from 7.6 MET-hrs.wk^{-1} to ≥22.8 MET-hrs.wk^{-1}; such doses are approximately the equivalent to ~120 to ~360 mins/wk of moderate-intensity exercise or 75 to 230 mins/wk of vigorous-intensity exercise.[45] Similarly, studies examining the relationship between post-diagnosis physical activity / exercise and breast cancer mortality reported 'beneficial' amounts range from 7.6 MET-hrs.wk^{-1} to ≥14.9 MET-hrs.wk^{-1} (~120 to ~250 mins/wk of moderate-intensity exercise or ~75 to ~150 mins/wk of vigorous-intensity exercise).[22] The minimum physical activity or exercise exposure associated with benefit is often not reported or emphasized, with focus primarily on the amount associated with the largest magnitude of risk reduction. Finally, clinical trials will be designed to test whether treating patients with a certain exercise dose (and schedule) impacts disease outcomes in *inactive* patients (selection of inactive patients is of obvious importance). Hence, the critical information required to adequately inform trial design is the *change* in exercise associated with disease outcomes; this data is currently not available since the vast majority of studies only assess exercise exposure at one timepoint. Interestingly, in an unplanned exploratory analysis of the Women's Healthy Eating and Living (WHEL) Study,[17] patients inactive at baseline (n=1,186) that subsequently met national guidelines at 1 year (i.e., at least 150 or 75 mins/wk of moderate or vigorous activity, respectively) via self-report was not associated with an improvement in breast cancer outcomes.[46]

In oncology drug development, the starting dose of new agents in first-in-human phase 0 studies is usually one-tenth of the maximum-tolerated dose (MTD) or dose-limiting toxicity in rodents; interspecies (animal to human) scaling factors are then applied to normalize to body-surface area and dosage in milligrams per kilogram.The recommended phase 2 dose (RP2D) of a particular agent is then further empirically derived from dose-finding phase 1 studies. The application of a comparable preclinical approach is not appropriate at present since similar interspecies scaling factors have not been identified for exercise. It could be argued that the exercise dose for definitive trial testing could be guided by the prescriptions tested in the numerous prevention and post-diagnosis RCTs investigating the effects of structured exercise training on alterations in various biomarkers or symptom control outcomes. Although these trials establish initial feasibility, tolerability and safety of exercise therapy in a given indication and setting (of particular importance in patients with cancer), this data is not sufficient or appropriate to guide the RP2D for therapeutic-intent trials. Indeed, the peril of this approach is observed in RCTs of established pharmacotherapeutics shown to exhibit minimal antitumor efficacy when repurposed on the basis of the originally

labeled indication.[47] The elucidation of standardized metrics to translate preclinical dosing to human exercise-oncology trials would represent a major advance in the field.

Regimen (Prescription) Characteristics:

Similar to systemic anticancer agents, the treatment regimen used to deliver the selected exercise dose will undoubtedly influence activity, feasibility, and safety. The major exercise regimen parameters are described in Table 2. A detailed discussion of how all the different elements of an exercise prescription may impact antitumor activity is beyond the scope of this article but has been reviewed elsewhere.[48,49] On the basis of limitations described in the prior section, information derived from observational studies is arguably of minimal value in guiding the dose and schedule of a particular exercise regimen to be evaluated in a specific definitive trial. Exercise-oncology RCTs have generally tested the efficacy of standard exercise prescriptions on changes in symptom control end points such as exercise capacity and patient-reported outcomes (e.g., 3 days/wk of aerobic exercise for 30 to 45 mins/sessions over 12 to 24 weeks).[48] However, using a prescription demonstrated to be efficacious for improving a non-tumor outcome symptom in a therapeutic-intent trial is problematic since it assumes the exercise load required to modulate both outcomes is the same.[49] In the setting of cardiovascular medicine, the efficacy of exercise (on different outcomes) differs as a function of the exercise dose, suggesting that in order to optimize benefit, a prescription should be targeted to the primary endpoint, system(s) or pathway(s) of interest.Rational dosing loads and schedules that modulate growth factors involved in specific oncogenic pathways could be tested in clinically relevant animal models prior to guide selection of exercise prescriptions for clinical investigation in pre-specified tumor subtypes.[49]

In summary, the outlined limitations reveal that neither the dose nor prescription regimen of exercise for testing in definitive trials can be empirically or accurately derived. Thus, selection of the RP2D on the basis of the current evidence will likely be imprecise.[43]

Predictors of Response

Closer inspection of exercise – cancer outcomes from meta- and pooled analyses of observational data reveal that results of individual studies are not consistent, with many reporting overlapping and wide 95% confidence intervals.[22,25] These data indicate considerable inter-patient heterogeneity in tumor response to exercise. Factors that may alter such a response can be broadly characterized into tumor-related and host-related factors.

Tumor-related factors.

Evaluation of the exercise – cancer pathogenesis relationship has broadly assumed that cancer is a genetic and physiologically homogeneous disease.[4] However, the impact of exercise may differ as a function of clinicopathologic features (e.g., tumor size, estrogen receptor status) in early-stage breast cancer,[50–52] whereas in colorectal cancer, tumor*PTGS2*positivity, CTNNB1 negativity, expression of CDKN1B (p27), and CD3+ cell density (infiltration) predict sensitivity to exercise.[53–56] In preclinical work, exercise inhibited, had no effect, or accelerated tumor growth compared with control in three distinct,

claudin-low, triple-negative breast cancer mouse models.[31] These data are contrary to the observational evidence indicating that exercise benefit may be confined to ER positive disease,[50] rather indicating exercise sensitivity may be subtype or molecular subtype independent. Clearly, such findings are hypothesis generating, requiring validation in independent cohorts and biologic confirmation in additional preclinical studies.

Host-related factors.

Host factors such as germline SNPs, circulating concentrations and function of immune surveillance phenotypes, inflammatory or metabolic effectors, and gut microbiota contribute to and/or modify the antitumor activity of conventional and novel agents.[57–61] A paucity of data is available on whether such factors predict exercise response. Nkondjock et al[62] found no association between physical activity and risk of breast cancer among *BRCA* mutation carriers, whereas King et al[63] found physical activity delayed/reduced the lifetime risks of ovarian cancer by 54% in *BRCA1* mutation carriers and 23% for *BRCA2* mutation carriers. To our knowledge, the predictive value of circulating host factors has not been investigated in any setting. Nevertheless, related work showed the antiproliferative effect of metformin differed as a function of pre-treatment circulating metabolic factors.[64,65]

At present, it is not yet possible to select which patients are the most likely to derive antitumor exercise benefit. Elucidation of such factors is important to inform patient selection and insights into personalization of exercise therapy.[48] Secondary analysis based on individual stratification variables (e.g., age, treatment, receptor status) will undoubtedly reveal subgroups predictive of exercise response.[66] However, this approach has a number of well-recognized limitations including treatment response / heterogeneity as optimally identified by stratification based on multiple rather than single variables, and are typically underpowered, and, is at best, hypothesis-generating as opposed to hypothesis-testing.[67]

Where to Go From Here?

As reviewed here, essential knowledge gaps related to (1) biological activity, (2) optimal dose and schedule, and (3) predictors of response currently impede the rational as well as optimal development of exercise as cancer treatment. Clearly, discoveries from observational and preclinical studies as well as anticipated results from ongoing definitive trials will provide insights into these gaps, however, the aforementioned inherent nature and associated limitations suggest that such data will likely be of limited value to optimally guide rational trial design. Hence, in addition to ongoing and planned work in early steps outlined in our development framework (i.e., (molecular) epidemiological, preclinical testing, and safety / feasibility clinical studies), the evidence base is sufficient to proceed to the next step - conduct of early phase 1/2-equivalent trials to identify the RP2D and predictors of response.

Consistent with phase 1 studies of contemporary oncology therapeutics,[68] the RP2D of exercise could be selected on the basis of feasibility / tolerability together with consideration of biological activity.[4] Phase 1a dose-finding / escalation studies offer a mechanism to identify the maximal feasible dose (MFD) of exercise using metrics adapted from oncology drug development. Specifically, feasibility can be evaluated using a combination of study attrition, adherence, and frequency of dose modifications and interruptions,[69,70] with safety

assessed using Common Terminology Criteria for Adverse Events (CTCAE). The threshold of acceptable feasibility and safety should be defined *a priori*. The types of correlative science markers used to evaluate biological activity (of identified feasible doses) are dependent on setting. For example, pre-surgical 'window of opportunity' studies provide a unique opportunity to test the biological activity of exercise in treatment-naïve patients using surrogates of tumor response (e.g., tumor cell proliferation, pathway modulation). Indeed, standard clinical practice paradigms in several oncologic settings offer the opportunity to test the biological activity of short-term (e.g., 4 to 6 week) exercise therapy during preoperative staging workup, or in longer-term (e.g., 4 to 6 month) during neoadjuvant therapy. If supported by preclinical studies, testing the additive effects of exercise to indicated conventional therapy in the neoadjuvant or metastatic setting provide alternative settings to assess biological activity as well as explore effects on established disease surrogates (pathological complete response, progression-free survival). In the setting of minimal residual disease, measurement of circulating tumor DNA can evaluate therapeutic response via quantification of mutational load (number of mutant DNA fragments in plasma). Acquisition of pre-treatment tissue specimens will be critical for discovery of novel genomic and clinical predictors of response. As in drug trials, dosing cohorts achieving the minimal feasibility criteria but exhibiting biological activity could be selected for further evaluation in safety / dose-expansion (phase 1b) testing. Other considerations in clinical testing of exercise are summarized in Table 3. A summary of the current evidence base, limitations, and recommended future directions are presented in Table 4.

Conclusion

Exercise therapy has significant promise to be a highly efficacious, low-toxicity, and cost-effective therapy to improve cancer risk and outcomes. Patients are also interested in the therapeutic potential of exercise – a strategy within patients' control that can potentially alter disease pathogenesis and symptomology without the adverse effects of conventional pharmacological agents. However, the majority of non-traditional therapies fail in definitive trials. We contend these failures provide critical lessons for the continued development of exercise as a candidate antitumor strategy. Indeed, persisting with the current approach used to develop and test non-traditional strategies may continue to yield null results, thereby potentiating the sentiment that such interventions (including exercise therapy or lifestyle interventions) are not effective means to reduce primary cancer incidence and progression. In this paper, we attempted to highlight some of the important knowledge gaps currently precluding optimal development of exercise as anticancer therapy as well as outline potential next steps. We hope these concepts provide one potential platform and approach to optimize the therapeutic promise of exercise therapy.

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Table 1.

Methods for measurement and quantification of physical activity in observational studies

Method	Example
Self-reported validated surveys used to measure physical activity and exercise	Participant recalls the average frequency (times/week) and duration (minutes/session) of different physical activity types, as appropriate, participated in over a distinct period of time (e.g., past 7 days or past month)
Intensity of each reported activity is weighted using the standardized classification of energy expenditure [METs])	One MET is the energy expenditure for sitting quietly for an hour (~3.5 $mL.kg^{-1}min^{-1}$)
MET values for specific activities are defined as the ratio of the metabolic rate of the activity divided by resting metabolic rate	Average pace walking has a MET value of 3 while jogging and running have MET values of 7 and 12, respectively
MET-hours per week for each activity are calculated from the reported hours per week for that activity weighted by the assigned MET value.	Data are summed to calculate total $MET\text{-}hrs.wk^{-1}$
Categorization of $MET\text{-}hrs.wk^{-1}$ varies across studies and no standardized classification system is currently in use	Physical activity levels categorized by quartile or quintile

Abbreviations: MET, metabolic equivalent task

Table 2.

Components of exercise prescription and ongoing phase 3 RCTs of structured exercise interventions

		Ongoing Phase 3 RCTs	
Component	**Description**	**INTERVAL[6]**	**CHALLENGE[5]**
Modality	Type of exercise	Structured resistance exercise and aerobic exercise	Recreational physical activity
Frequency	Treatment sessions per week	3 sessions per week	Increase by at least 10 MET-hrs.wk^{-1} to maximum of 27 MET-hrs.wk^{-1}
Intensity	Dose intensity of each treatment (i.e. mild to vigorous)	High and moderate intensity sessions	Varies
Duration	Length of each treatment session	Varies	Varies
Length	Total period of treatment exposure	24 months	36 months
Schedule	Linear (each session performed at the same intensity) or non-linear (intensity is continually altered and progressed)	Non-linear	Linear
Setting	Supervised versus unsupervised, facility- versus home based	Supervised, facility-based x12 months; unsupervised, home-based for subsequent 12 months	Supervised, facility-based sessions for at least 6 months plus unsupervised sessions
Delivery	One-on-one, group-based, or remote via telemedicine	One-on-one x12 months, self-managed for subsequent 12 months	One-one-on or group-based

Abbreviations: RCT, randomized control trial; INTERVAL, Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer; CHALLENGE, Colon Health and Life-Long Exercise Change; MET, metabolic equivalent task.

Table 3.

Other key considerations in exercise oncology clinical trials

Consideration	Description
Dose quantification	• Complete description of the exercise intervention is required and includes full reporting of exercise prescription and principles of training.[71]
Novel trial designs	• Adaptive trial designs in which pre-planned modifications are made based on interim feasibility data may be more appropriate for investigations of longer-term interventions such as exercise, than traditional dose escalation designs (e.g., "3 + 3"). • The continual reassessment method is an adaptive design that utilizes a model-based approach for phase 1 studies and allows for the consideration of toxicities that may occur late in the observation period.[72–74]
Biological activity	• Markers of pharmacokinetic activity traditionally used to evaluate new drug compounds are of limited value for the assessment of exercise; biological activity should be evaluated by pharmacodynamic assessments.
Quality reporting	• Conduct and reporting of clinical trials must adhere to high-level quality standards in order to optimize interpretation, reproducibility, and translation into clinical practice. • In drug development, the implementation of the Consolidated Standards of Reporting Trials (CONSORT) led to marked improvements in RCT rigor, standardization, and conduct.[75,76] • CONSORT guidance has been extended to non-pharmacologic trials (CONSORT-NPT) to account for behavioral interventions, however current guidelines are suboptimal for exercise trials since they do not provide a standardized mechanism for reporting all exercise prescription components. • Adherence to quality standards can be encouraged by regulatory oversight (not currently mandated for non-pharmacologic trials including exercise).
Implementation	• Effective implementation strategies are needed in which exercise dose and compliance can be accurately quantified whilst optimizing patient convenience.[77]Innovative strategies for effective exercise implementation are needed. Digitized and telemedicine platforms offer a promising opportunity to leverage technological advances for standardized delivery of exercise interventions in a patient-centered manner.

Table 4.

Summary of current evidence, limitations, and future directions in exercise oncology

Current evidence
• Observational data support an association between higher physical activity levels and lower risk of several cancers including colon, breast, kidney, endometrial, bladder, esophagus (adenocarcinoma), gastric (cardia), and lung.
• Observational data support an association between increased post-diagnosis physical activity and lower disease-specific mortality for breast, colon, and prostate cancers.
• Limited preclinical data support antitumor activity of exercise in murine or human models of cancer.
• Data from RCTs support a benefit of exercise on patient reported outcomes and symptom control endpoints in cancer populations.
Limitations
• Physical activity only assessed by self-report at a single time-point in observational studies.
• A broad range of physical activity / exercise ‘doses’ associated witd reductions in primary cancer risk or cancer-related mortality.
• Biological activity (e.g., effects on tumor or tumor microenvironment) not known.
• Predictors of response (e.g., clinicopatdologic features, tumor subtype, genomic signatures) not known.
Future directions
• Preclinical or “co-clinical” testing demonstrating modulation of tissue and tumor markers in relevant animal models
• Conduct of early phase dose-finding / dose-escalation trials to identify feasible doses of exercise in the target population and setting (i.e., phase 1a)
• Correlative science studies to examine biological activity of the identified feasible exercise doses.
• Confirmation of feasibility and evaluation of preliminary antitumor efficacy in safety / dose-expansion (phase 1b) testing.
• Determination of the recommended phase 2 dose based on feasibility and biological activity.