Review

Clinical Cancer Research

Physical Activity and Cancer Outcomes: A Precision Medicine Approach

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Abstract

There is increasing interest in applying a precision medicine approach to understanding exercise as a potential treatment for cancer. We aimed to inform this new approach by appraising epidemiologic literature relating postdiagnosis physical activity to cancer outcomes overall and by molecular/genetic subgroups. Across 26 studies of breast, colorectal, and prostate cancer patients, a 37% reduction was seen in risk of cancer-specific mortality, comparing the most versus the least active patients (pooled relative risk = 0.63; 95% confidence interval: 0.54–0.73). Risks of recurrence or recurrence/cancer-specific death (combined outcome) were also reduced based on fewer studies. We identified ten studies of associations between physical activity and cancer outcomes by molecular or genetic markers. Two studies showed statistically significant risk reductions in breast cancer mortality/recurrence for the most (versus least) physically active estrogen receptor–positive/progesterone receptor–positive (ER^+/PR^+) patients, while others showed risk reductions among ER^-PR^- and triple-negative patients. In colorectal cancer, four studies showed statistically significant risk reductions in cancer-specific mortality for patients with high (versus low) physical activity and P21 expression, P27 expression, nuclear $CTNNB1^-$, PTGS2 $(COX\text{-}2)^+$, or IRS1 low/negative status. One prostate cancer study showed effect modification by Gleason score. As a means to enhance this evidence, future observational studies are needed that will measure physical activity objectively before and after diagnosis, use standardized definitions for outcomes, control for competing risks, assess nonlinear dose–response relations, and consider reverse causality. Ultimately, randomized controlled trials with clinical cancer outcomes and a correlative component will provide the best evidence of causality, relating exercise to cancer outcomes, overall and for molecular and genetic subgroups. *Clin Cancer Res; 22(19); 4766–75. ©2016 AACR.*

Introduction

Precision medicine is an emerging approach in oncology that attempts to address the substantial variability in individual patient response to cancer therapy (1). Although precision medicine recognizes that many factors can contribute to this heterogeneity, its primary contribution is to highlight the potential role of genetic and molecular factors based on an improved understanding of cancer biology. The primary goal of precision medicine is to give an intervention to patients who will benefit and avoid providing it to patients who will either not benefit or be harmed. A secondary goal is to avoid the side effects and costs of giving the intervention to patients who will either not benefit or who will be harmed.

Exercise oncology researchers have recognized the substantial variability in patient response to exercise interventions and have sought to understand these differences (2–4). Similar to research on medical oncology, most of the variables examined as predictors of exercise response have been demographic and clinical factors. Unlike medical oncology, however, most of the outcomes (responses) examined by exercise oncology researchers have been health-related fitness outcomes and patient-reported outcomes, not cancer outcomes. The increasing interest in cancer outcomes by exercise oncology researchers makes the application of precision medicine (i.e., the focus on genetic and molecular subgroups) much more relevant (5). Nevertheless, some differences between exercise and medical interventions may have implications for the application of precision medicine to exercise oncology.

First, exercise is a limited number of "medicines" (e.g., aerobic, strength, balance, and flexibility) that have already been developed and thoroughly tested in many populations for many outcomes. Consequently, an improved understanding of cancer biology is unlikely to lead to new "exercise drug" development. What an improved understanding of cancer biology may do, however, is facilitate the development of targeted exercise prescriptions (e.g., dose, scheduling, and timing) for improving cancer outcomes by matching the known biological effects of exercise with the new understanding of cancer biology. Such targeted exercise prescriptions based on biology may have a greater likelihood of success in improving cancer outcomes.

Second, exercise has so many other health benefits for cancer patients, so few side effects, and so little cost that it is unlikely

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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that many cancer patients would ever be recommended not to exercise. Consequently, avoiding side effects and financial costs in patients who do not benefit in terms of improved cancer outcomes does not seem like a major benefit of the precision medicine approach in exercise oncology. One possible scenario in which exercise might not be recommended would be if exercise is shown to have a deleterious effect on cancer outcomes. To date, however, there is no evidence suggesting that exercise may worsen cancer outcomes. Moreover, exercise can (only) be self-administered and, therefore, unlike medical interventions it is not possible to withhold exercise from cancer patients even if it was not indicated, although cancer professionals could certainly recommend against it.

Perhaps the greatest promise of precision medicine for exercise oncology is that a new understanding of cancer biology may lead to the identification of genetic or molecular subgroups of patients who are particularly benefitted (or harmed) by specific exercise prescriptions. If such subgroups could be identified, it is likely that such patients would be highly motivated to perform (or avoid) the targeted exercise prescription. Moreover, it is possible that cancer centers and/or health insurance companies would be willing to fund such exercise interventions for subgroups of patients with substantial benefit.

In 2015, Jones (5) proposed a multidisciplinary, multistaged translational research agenda for precision exercise in cancer treatment. The first steps in this framework involve evaluating causality from observational research and generating hypotheses from molecular epidemiology studies. The purpose of this article is to lay a foundation for this exciting new area of precision oncology by appraising the current observational epidemiologic evidence overall and from a precision exercise perspective. We begin with a review of epidemiologic studies that have examined postdiagnosis physical activity in relation to cancer recurrence or survival and consider the causal nature of the findings, as initial "discovery" steps in translational development (5). We then review molecular epidemiology studies that examined associations between physical activity and cancer outcomes by genetic or molecular subtypes. We make recommendations for future research and highlight ongoing studies that could enhance the current body of evidence. We finally provide an overview of the types of epidemiologic studies that can guide tumor marker selection for precision exercise research.

Observational Evidence

Postdiagnosis physical activity and cancer survival

To identify all studies of postdiagnosis physical activity and cancer recurrence or cancer-specific survival (any cancer site), we searched PubMed up to March 2016. Several keywords and Medical Subject Heading terms were applied (Supplementary Table S1) corresponding to physical activity and cancer-related outcomes. We abstracted fully adjusted risk estimates for the highest versus the lowest levels of postdiagnosis physical activity in relation to one or more cancer survival outcomes, except all-cause mortality, which was excluded from this review. If multiple activity types/units were examined in the same study, we gave preference to recreational physical activity in MET-hours/week. We used random-effects models (6) to derive pooled estimates of risk using Stata v.13.

Twenty-six prospective cohort studies were identified with reported associations between postdiagnosis physical activity level and cancer survival outcomes. The first study was published in 2004 (7), and 18 (8–25) out of 26 studies were published within the past 5 years. Cancer-specific mortality was examined in 21 studies (refs. 7–21, 26–31; Table 1). The pooled risk reduction across all studies was 37% [RR = 0.63, 95% confidence interval (CI), 0.54–0.73] when comparing the most versus the least active participants. Most of these studies were on breast cancer (7–12, 26–29), followed by colorectal cancer (13–16, 30, 31), prostate cancer (17–19), and mixed cancers (20, 21). In 11 (8, 10, 11, 13, 14, 17, 18, 20, 26, 27, 31) of the 21 cancer-specific studies, a statistically significant risk reduction was seen with higher levels of physical activity. Another analysis from the After Breast Cancer Pooling Project (ABCPP; ref. 32) combined data from four studies [shown separately in Tables 1 and 2 (22, 24, 27, 29)] to examine the association between meeting physical activity guidelines and subsequent cancer survival. That project revealed a 25% risk reduction (RR = 0.75; 95% CI, 0.65–0.85) for breast cancer–specific mortality (32) and a 22% higher risk of breast cancer–specific mortality for women with very low (<1.5 MET-hours/week) versus higher activity levels (33).

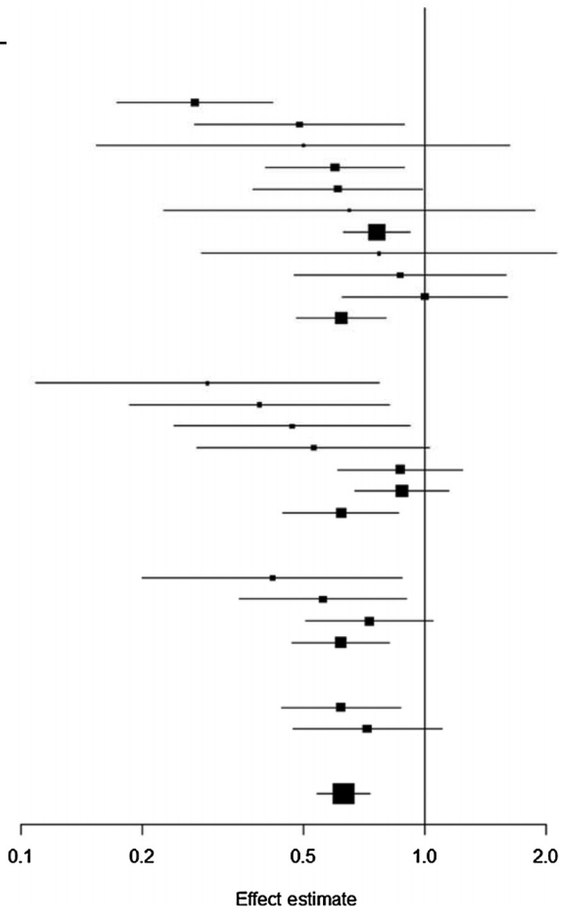
Only eight studies (18, 22–25, 27, 29, 34) included cancer recurrence as an outcome (Table 2). In these studies, recurrence was examined alone (22, 30), combined with cancer-specific deaths (23–25, 27, 29), or combined with progression (refs. 18, 23; see Supplementary Table S2). In two studies (27, 29), death due to breast cancer (with no reported recurrence) was assumed to be a recurrent event. Given inconsistent recurrence definitions across studies, the pooled risk reduction of 35% (RR = 0.65; 95% CI, 0.56–0.75) must be interpreted with caution. The ABCPP found no association between meeting physical activity guidelines and risk of breast cancer recurrence (RR = 0.96; 95% CI, 0.86–1.06; ref. 32).

In summary, there appeared to be a protective association between postdiagnosis physical activity and cancer-specific mortality, with pooled risk reductions of 38% for breast, colorectal, and prostate cancers, respectively. These studies were all prospective cohorts with the assessment of physical activity following diagnosis and preceding cancer outcomes. Almost all observational studies excluded cancer patients who experienced an outcome shortly after physical activity assessment, except for two (7, 29). This exclusion addressed possible reverse causation as postdiagnosis physical activity can be influenced by the severity of disease and by cancer treatment, which in turn influence recurrence and survival. Eighteen (11–14, 17, 18, 20–24, 26–31, 34) of 26 studies tested for a dose–response relationship between increasing levels of physical activity and decreasing risk of mortality, and just over half (11, 13, 14, 17, 18, 20, 21, 24, 27, 30, 31, 34) revealed a statistically significant linear trend. No studies considered nonlinear dose–response relations. One previous meta-analysis (35) showed a 16% reduction in cancer-specific mortality risk for every 15 MET-hours/week increase in postdiagnosis physical activity.

Limitations of the research conducted to-date need to be considered when interpreting this literature. First, measurement error may exist in these studies because of misreporting physical activity, except in the clinical trial by Courneya and colleagues (25) in which exercise was prescribed and

Table 1. Individual and pooled risk estimates from prospective cohort studies that related postdiagnosis physical activity to cancer-specific mortality, by cancer site

Author, year	No. of events/cases	Effect estimate	95% CI
Breast			
Bradshaw, 2014 (10)	195/1,033	0.27	0.17–0.42
Holick, 2008 (26)	109/4,482	0.49	0.27–0.89
Borch, 2015 (9)	155/1,327	0.50	0.15–1.62
Holmes, 2005 (27)	280/2,987	0.60	0.40–0.89
Irwin, 2011 (11)	86/2,910	0.61	0.38–0.99
Irwin, 2008 (28)	115/933	0.65	0.23–1.87
Williams, 2014 (8)	46/986	0.76	0.63–0.92
de Glas, 2014 (12)	39/435	0.77	0.28–2.12
Sternfield, 2009 (29)	102/1,970	0.87	0.48–1.59
Borugian, 2004 (7)	112/603	1.00	0.63–1.60
Pooled estimate ($I^2 = 61.3\%$)	1,239/17,666	0.62	0.48–0.80
Colorectal			
Kuiper, 2012 (13)	51/606	0.29	0.11–0.77
Meyerhardt, 2006 (30)	80/573	0.39	0.19–0.82
Meyerhardt, 2009 (31)	88/661	0.47	0.24–0.92
Arem, 2015 (14)	128/3,797	0.53	0.27–1.03
Campbell, 2013 (15)	379/2,236	0.87	0.61–1.24
Baade, 2011 (16)	345/1,825	0.88	0.67–1.15
Pooled estimate ($I^2 = 56.6\%$)	1,071/9,698	0.62	0.45–0.86
Prostate			
Kenfield, 2011 (17)	112/2,705	0.42	0.20–0.88
Friedenreich, 2016 (18)	170/830	0.56	0.35–0.90
Bonn, 2015 (19)	194/4,623	0.73	0.51–1.05
Pooled estimate ($I^2 = 0.8\%$)	476/8,158	0.62	0.47–0.82
Any			
Lee, 2014 (20)	337/1,021	0.62	0.44–0.87
Inoue-Choi, 2013 (21)	184/2,017	0.72	0.47–1.10
Overall			
Pooled estimate ($I^2 = 47.9\%$)	3,307/38,560	0.63	0.54–0.73



supervised. The observational studies used interviewer-administered questionnaires (10, 24, 28), self-administered questionnaires (7–9, 11–17, 19–23, 26, 27, 29–31, 34), or a combination (18). Some studies measured current physical activity behavior only (e.g., past week; refs. 7–9, 11, 13, 15, 16, 20–22, 30) which may not capture habitual activity levels. Only four studies controlled for prediagnosis physical activity (9, 14, 17, 18) and none adjusted for sedentary behavior in their statistical models, which could influence this association (33, 35). Only five studies (12, 17, 18, 25) accounted for competing risks in their analyses. Definitions of recurrence as an outcome were inconsistent.

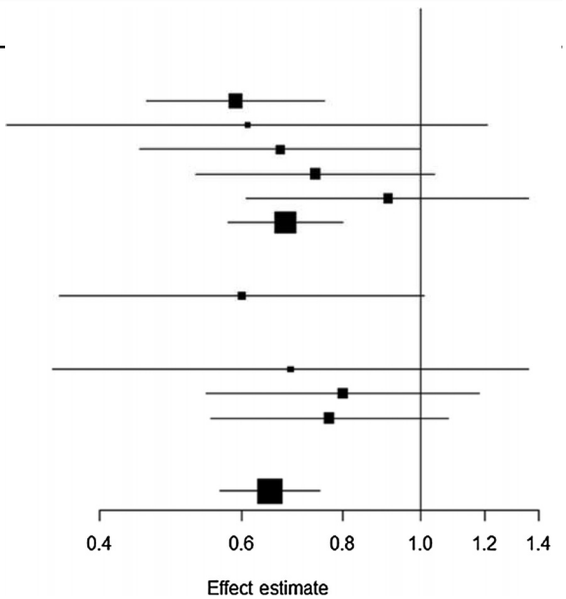
Associations in molecular subgroups

We located ten published reports that have related cancer-specific survival outcomes to postdiagnosis physical activity stratified by molecular subtypes (Table 3). Breast cancer patients were examined in four observational reports (10, 24, 27, 36) and in one exploratory analysis of a clinical trial (25). Three studies showed survival benefit for more physically active estrogen receptor–positive (ER^+; ref. 25) or ER^+ or progesterone receptor–positive (PR^+; refs. 10, 27) breast cancer patients; two were statistically significant (10, 27). However, a pooled dataset of ER^+ patients in the United States (37) revealed little benefit from physical activity with respect to late recurrence (≥5 years; HR = 0.89; 95% CI, 0.73–1.09). In the Shanghai Breast Cancer Survival Study, a 64% lower risk of recurrence/breast cancer–specific mortality was observed for the most active versus the least active ER^-PR^- patients (24); triple-negative patients (i.e., ER^-PR^- and no HER2 overexpression) showed a 46% lower risk (36). None of the studies summarized in Table 3 showed a statistically significant interaction by ER/PR status. Notably, in the clinical trial reported by Courneya and colleagues (25), sample size was limited and there were only 37 events on which to base the recurrence-free interval analysis. That trial also showed a large, non–statistically significant risk reduction of 79% among HER2-positive breast cancer patients assigned to exercise versus controls during chemotherapy.

Four reports (38–41) described participants from the Nurses' Health Study and Health Professionals Follow-up Health Study with respect to postdiagnosis physical activity and colorectal cancer–specific mortality, stratified by molecular subtype. Meyerhardt and colleagues (39) explored six molecular targets; Morikawa and colleagues (40) analyzed nuclear CTNNB1 status;

Table 2. Individual and pooled risk estimates from prospective cohort studies that related postdiagnosis physical activity to cancer recurrence or progression (defined in Supplementary Table S2), by cancer site

Author, year	No. of events/cases	Effect estimate	95% CI
Breast			
Chen, 2011* (24)	450/4,826	0.59	0.46–0.76
Courneya, 2014* (25)	37/242	0.61	0.31–1.21
Bertram, 2011 (22)	295/2,361	0.67	0.45–1.00
Holmes, 2005* (27)	370/2,987	0.74	0.53–1.04
Sternfield, 2009* (29)	225/1,970	0.91	0.61–1.36
Pooled estimate ($I^2 = 0\%$)	1,377/12,386	0.68	0.58–0.80
Colorectal			
Meyerhardt, 2006 (30)	159/832	0.60	0.36–1.01
Prostate			
Richman, 2011* (23)	117/1,455	0.69	0.35–1.36
Friedenreich, 2016 (18)	239/830	0.80	0.54–1.18
Pooled estimate ($I^2 = 0\%$)	356/2,285	0.77	0.55–1.08
Overall			
Pooled estimate ($I^2 = 10\%$)	1,892/15,298	0.65	0.56–0.75



NOTE: Asterisks indicate studies in which recurrences/progressions and cancer-specific deaths were combined and analyzed as a single outcome.

Yamauchi and colleagues studied PTGS2 (COX-2) expression (41); and Hanyuda and colleagues (38) studied IRS1. Across the four reports, statistically significant risk reductions were found, suggesting benefit from physical activity, for subgroups of colorectal cancer survivors expressing P21 (HUGO gene nomenclature approved symbol: CDKN1A) or P27 (HUGO gene nomenclature approved symbol: CDKN1B; ref. 39), or with nuclear $CTNNB1^{-}$ (40), PTGS2 $(COX\text{-}2)^{+}$ (41), or IRS1 low/negative (38) status.

One report (23) described a statistically significant interaction among Gleason score, walking duration, and prostate cancer progression (Table 1). In other prostate cancer survival studies, statistical interactions with Gleason score were not tested (19) or were not statistically significant (results not shown; refs. 17, 18).

Future Research

Enhancing the observational evidence

Given that the first study was published in 2004 and only 26 studies were identified to-date that have examined some aspect of physical activity and its relation to cancer survival outcomes, there is an overall paucity of evidence for most cancer sites. For this reason it would be necessary to investigate causal associations in cancers besides colorectal and breast. Specific aspects of the study design and analysis also warrant particular attention in future research. The following needs have been identified: (i) to measure physical activity and sedentary behavior objectively; (ii) to consider the impact of sedentary behavior and prediagnosis physical activity on postdiagnosis associations (prediagnosis activity may or may not correlate with postdiagnosis activity, and is associated with a decreased risk of cancer-related death in the general population; ref. 42); (iii) to control for competing risks for mortality in the statistical analyses; (iv) to assess nonlinear dose–response relationships to determine whether any threshold levels of physical activity exist beyond which no additional survival benefit exists; (v) to assess the possibility that reverse causality exists in these studies, for example, by excluding deaths within close proximity to physical activity assessment; (vi) to use standardized definitions for all outcomes, including recurrences and progressions; and (vii) to replicate and explore additional tumor markers in large-scale molecular epidemiologic studies.

Ongoing studies have the potential to address some of these research gaps. One project of note is our Alberta Moving Beyond Breast Cancer (AMBER) cohort study (43). The primary aim of this study is to examine the associations and biologic/molecular mechanisms among objectively measured physical activity, sedentary behavior, health-related fitness, and breast cancer outcomes. We are recruiting 1,500 newly diagnosed breast cancer cases in Alberta and assessing all of these parameters at four time points from diagnosis to 5 years after diagnosis. All women are followed for an additional 5 years, and all treatments, tumor characteristics, and cancer outcomes are assessed during follow-up. The AMBER cohort study was specifically designed to overcome the methodologic limitations that existed with previous observational epidemiologic studies, including objective measures of physical activity and sedentary behavior, a comprehensive assessment of health-related fitness, blood collection at multiple time points, a full assessment of treatment and clinical variables, and a large sample size to permit subgroup analyses. Extensive data on tumor characteristics will be available for these study participants that will be used to examine associations within molecular subgroups. The study baseline recruitment will be completed in 2018, with follow-up assessments done by 2023.

Table 3. Molecular epidemiology studies that assessed postdiagnosis physical activity in relation to cancer survival and also stratified by tumor subtype

Study overview[a]	Physical activity assessment	Participants	Subgroup effect estimates
Breast cancer–specific mortality			
Holmes, 2005 Nurses' Health Study (27). Median follow-up, 8 years No. of events/cases: 280/2,987	Self-administered questionnaire. Leisure-time physical activity, mostly moderate-vigorous. Past year physical activity assessed every 2 years; only the first measurement taken at least 2 years after breast cancer diagnosis was used for analysis.	Women, ages 38–63 years with breast cancer: Stage I, 57.9% Stage II, 35.0% Stage III, 7.1% Median time of recruitment, 38 months postdiagnosis.	Physical activity, 9+ vs. <9 MET-hrs/wk RR (95% CI), breast cancer-specific mortality: ER^+PR^+: 0.50 (0.34–0.74) ER^-PR^-: 0.91 (0.43–1.96) $P_{interaction} = 0.08$
Bradshaw, 2014 Long Island Breast Cancer Study Project (10) Followed 13 yrs; median survival 12.7 years No. of events/cases: 195/1,436	By interview. 12-month recreational physical activity done each year since diagnosis (for up to 7 years). Interview was approximately 5 years postdiagnosis.	Women, mean age of 58.8 years with *in situ* or invasive breast cancer. Recruited approximately 5 years postdiagnosis.	Physical activity in two categories vs. none 1) 0.1–9.1 vs. 0 MET-hrs/wk 2) >9 vs. 0 MET-hrs/wk HR (95% CI), breast cancer-specific mortality: ER^+PR^+: 0.07 (0.00–0.44) 0.18 (0.08–0.36) ER^- or PR^-: 0.47 (0.12–1.33) 0.38 (0.19–0.72) $P_{interaction}$ not reported
Recurrence or breast cancer-specific mortality			
Chen, 2011 (24) Shanghai Breast Cancer Survival Study. Median follow-up, 4.3 years No. of events/cases: 450/4,511 (recurrence analysis)	By interview. Past 6 months exercise repeated up to three times (6 months, 12–18 months, 36 months postdiagnosis).	Women, mean age of 53.5 years with breast cancer: Stage I, 34.8% Stage IIa, 33.9% Stage IIb, 9.4% Stage III, 4.7% Approximately 6 months postdiagnosis	Exercise in two categories vs. none 1) <8.3 vs. 0 MET-hrs/wk 2) 8.3+ vs. 0 MET-hrs/wk HR (95% CI), relapse/disease-specific mortality: ER^+PR^+: 0.72 (0.47–1.12) 0.79 (0.53–1.19); $P_{trend} = 0.540$ ER^-PR^-: 0.40 (0.25–0.63) 0.36 (0.24–0.56); $P_{trend} = 0.002$ ER^+PR^- or ER^-PR^+: 0.62 (0.32–1.23) 0.51 (0.27–1.00); $P_{trend} = 0.166$ $P_{interaction} = 0.375$
Courneya, 2014 (25) Supervised Trial of Aerobic versus Resistance Training. Median follow-up, 7.4 years (89 months) No. of events/cases: 37/242	Intervention: 18 weeks of supervised exercise during chemotherapy. $N = 78$ aerobic; $N = 82$ resistance; $N = 82$ controls. Aerobic exercise 3 times/wk, up to 80% VO_{2max} by week 12, 45 minutes/session by week 18. Resistance exercise 3 times/wk; two sets of 8–12 repetitions of 9 different exercises at 60%–70% estimated 1-RM. Resistance increased by 10% after reaching >12 repetitions.	Women, 54.5% age of <50 years with breast cancer: Stage I: 24.8% Stage IIa: 40.9% Stage IIb: 19.8% Stage IIIa: 14.5% Pre-chemotherapy, within 6–8 weeks of diagnosis	Exercise (aerobic or resistance) vs. controls HR (95% CI), recurrence/breast cancer death (recurrence-free interval analysis): ER^+: 0.52 (0.23–1.16) ER^-: 0.85 (0.28–2.52) Luminal: 0.70 (0.26–1.85) $HER2^+$: 0.21 (0.04–1.02) Triple negative: 1.17 (0.31–4.37) $P_{interactions}$ not reported
Bao, 2015 (36) Shanghai Breast Cancer Survival Study. Median follow-up, 9.1 years No. of events/cases: 112/518	By interview. Past 6 months exercise repeated up to four times (6 months, 12–18 months, 36 months, 60 months postdiagnosis).	Women, mean age of 53.4 years with breast cancer: Stage I: 31% Stage II: 56% Stage III: 10% Unknown: 3% Approximately 6 months postdiagnosis	Exercise in two categories vs. none 1) <7.6 vs. 0 MET-hrs/wk 2) 7.6+ vs. 0 MET-hr/wk HR (95% CI), recurrence/disease-specific mortality: Triple negative: 0.64 (0.39–1.07) 0.54 (0.35–0.84); $P_{trend} = 0.01$ $P_{interaction}$ not applicable
Colorectal cancer-specific mortality			
Meyerhardt, 2009 (39) Nurses' Health Study & Health Professionals' Follow-up Study. Followed up to 20 years (1986–2006) No. of events/cases: 50/484	Self-administered questionnaire. Leisure-time physical activity, mainly moderate-vigorous. Past year physical activity; one assessment 1–4 years postdiagnosis.	Men and women, median age of 68 years with colorectal cancer: Stage I, 28.2% Stage II, 41.2% Stage III, 25.6% Unknown, 5% Diagnosed past 2 years	Physical activity, ≥18 vs. <18 MET-hrs/wk HR (95% CI), colorectal cancer–specific mortality: FASN-: 0.61 (0.30–1.25) FASN+: 0.95 (0.11–8.06); $P_{interaction} = 0.77$ *KRAS* wild-type: 0.71 (0.28–1.82) *KRAS* mutation: 0.42 (0.15–1.18); $P_{interaction} = 0.59$

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Table 3. Molecular epidemiology studies that assessed postdiagnosis physical activity in relation to cancer survival and also stratified by tumor subtype (Cont'd)

Study overview[a]	Physical activity assessment	Participants	Subgroup effect estimates
			P53$^-$: 0.46 (0.16–1.35) P53$^+$: 0.64 (0.26–1.59); $P_{interaction} = 0.58$ P21 lost: 0.87 (0.42–1.81) P21 expressed: 0.10 (0.01–0.98); $P_{interaction} = 0.19$ P27 lost: 1.40 (0.41–4.72) P27 expressed: 0.32 (0.12–0.85); $P_{interaction} = 0.03$ *PI3KCA* wild-type: 0.59 (0.26–1.33) *PI3KCA* mutation: 1.25 (0.25–6.40); $P_{interaction} = 0.96$
Morikawa, 2011 (40) Nurses' Health Study & Health Professionals' Follow-up Study. Median follow-up, 11.8 years No. of events/cases: 266/955 (68/497 for analysis)	Self-administered questionnaire. Leisure-time physical activity, mainly moderate-vigorous. Past year physical activity; one assessment 1–4 years postdiagnosis.	Men and women, mean age of 67.1 years with colorectal cancer: Stage I: 23.5% Stage II: 29.2% Stage III: 26.9% Stage IV: 12.9% Unknown: 7.5% Analysis was based only on stage I, II, III cases diagnosed in past 2 years	Physical activity, ≥18 vs. <18 MET-hrs/wk HR (95% CI), colorectal cancer-specific mortality: nuclear CTNNB1$^-$: 0.33 (0.13–0.81) nuclear CTNNB1$^+$: 1.07 (0.50–2.30) $P_{interaction} = 0.05$
Yamauchi, 2013 (41) Nurses' Health Study & Health Professionals' Follow-up Study Median follow-up, 11.9 years No. of events/cases: 89/605	Self-administered questionnaire. Leisure-time physical activity, mainly moderate-vigorous. Past year physical activity; one assessment 1–4 years postdiagnosis.	Men and women, mean age 67.3 years with colorectal cancer: Stage I: 27% Stage II: 35% Stage III: 27% Unknown: 11% Diagnosed past 2 years	Physical activity, three categories vs. none: 1) Q2 vs. Q1 2) Q3 vs. Q1 3) Q4 vs. Q1 HR (95% CI), colorectal cancer–specific mortality: PTGS2 (COX-2)−: 0.89 (0.32–2.51) 1.14 (0.42–3.08) 0.85 (0.27–2.67); $P_{trend} = 0.84$ PTGS2 (COX-2)+: 0.30 (0.14–0.62) 0.38 (0.20–0.71) 0.18 (0.08–0.41); $P_{trend} = 0.0002$ $P_{interaction} = 0.024$
Hanyuda, 2016 (38) Nurses' Health Study & Health Professionals' Follow-up Study Median follow-up, 15.1 year No. of events/cases: 52/371	Self-administered questionnaire. Leisure-time physical activity, mainly moderate-vigorous. Past year physical activity; one assessment 1–4 years postdiagnosis.	Men and women, mean age of 67.6 years with colorectal cancer: Stage I: 28% Stage II: 40% Stage III: 33% Diagnosed past 2 years	Physical activity, ≥18.3 vs. <18.3 MET-hrs/wk HR (95% CI), colorectal cancer–specific mortality: IRS1 neg/low: 0.39 (0.17–0.82) IRS1 high: 1.32 (0.50–3.53) $P_{interaction} = 0.005$
Prostate cancer progression			
Richman, 2011 (23) The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). Median follow-up, 22 months No. events/cases: 117/1,455	Self-administered questionnaire. Leisure-time physical activity including walking. Past year physical activity; one assessment, median 27 months postdiagnosis.	Men, mean age of 65 years with clinically localized prostate cancer: Stage T1: 55% Stage T2: 45% Recruited at diagnosis	Walking duration, ≥7 hrs/wk ($n = 15$ events) vs. <0.5 hrs/wk ($n = 25$ events) HR (95% CI), prostate cancer progression: Gleason sum <7: 0.39 (0.11–1.41) Gleason sum ≥7: 1.33 (0.54–3.29) $P_{interaction} = 0.006$

Abbreviations: CTNNB1, cadherin-associated protein β 1 (β-catenin); FASN, fatty acid synthase; IRS1, insulin receptor substrate 1; MET-hrs/wk, metabolic equivalent-hours of physical activity per week; neg, negative; PI3KCA, phosphatidylinositol 3-kinase; PTGS2, symbolizes COX-2; Q1, Q2, Q3, Q4, quartiles 1 to 4 cut-points in the distribution of physical activity; RM, repetition maximum; triple negative, the combination of ER$^-$PR$^-$ and no HER2 overexpression.
[a]Associations with all-cause mortality were not included in this review.

Another large-scale, ongoing, Pan-Canadian cohort study of note is the Reducing Breast Cancer in Young Women (RUBY) cohort study (44) that began in 2015 in 29 centers across Canada. This prospective cohort study is recruiting 1,200 women with newly diagnosed, incident breast cancer who are under the age of 40 years at diagnosis. These participants are completing extensive online questionnaires, providing blood samples, and are reassessed at 1 and 3 years after diagnosis with additional

questionnaires and blood collections. Several subprojects embedded in this study are targeting a range of clinical and epidemiologic research questions. One subproject is specifically focused on lifestyle factors with a comprehensive assessment of physical activity, sedentary behavior, and dietary intake. This study will also provide detailed data on molecular and tumor characteristics that will be combined with the lifestyle data.

Randomized trials are being conducted that will address limitations of even the best-designed observational studies; namely, reverse causation and confounding. Randomized trials provide stronger evidence of causality and contribute to our understanding of the biological mechanisms relating exercise to cancer outcomes. For example, the Colon Health and Lifelong Exercise (CHALLENGE) Trial is the first randomized controlled trial that is examining whether a 3-year exercise intervention in colon cancer survivors will improve their survival after cancer (45, 46). This trial is currently ongoing in over 50 centers worldwide with the objective of recruiting 962 participants and will provide the first definitive data on whether physical activity can improve survival. Correlative studies have been embedded in this trial that will be examining numerous hypothesized biomarkers associated with physical activity and survival.

Selecting tumor markers

In the design of molecular epidemiology studies, a tumor marker may be selected for investigation for several reasons. For instance, a tumor marker may represent a biological mechanism through which exercise improves cancer survival and its presence or absence predicts efficacy (analogous to a drug). In this case, several types of epidemiologic evidence can inform tumor marker selection (Fig. 1).

First, prospective cohort or case–control studies of cancer patients can complement preclinical research in clarifying the biological mechanisms influencing cancer survival (Fig. 1, #1). The mechanisms most often studied in exercise oncology include sex hormones, insulin-related pathways, and low-level chronic inflammation. Oxidative stress, immune function, and adipokines are commonly studied (47–49), and sarcopenia has been investigated (50, 51). However, the relative influence of each pathway and their combined effects (52) on cancer survival are unknown. If one pathway were more influential, this situation might justify studying a particular tumor marker over another. The clear overlap between these mechanisms and those for obesity and cancer are also noteworthy, which raises the question of whether a lifestyle intervention designed to induce weight loss might provide greater survival benefit than exercise alone, at least for some tumor subtypes.

Second, randomized controlled trials of exercise can be used to demonstrate exercise modes of action in humans using cancer survival biomarkers as endpoints (Fig. 1, #2). These trials, along with preclinical studies (53), can help demonstrate a coherent causal pathway, with exercise changing biomarkers in the right direction, to justify studying a tumor marker. Exercise trials in cancer patients (reviewed in refs. 54, 55) have typically measured changes in: insulin, glucose, adipokines

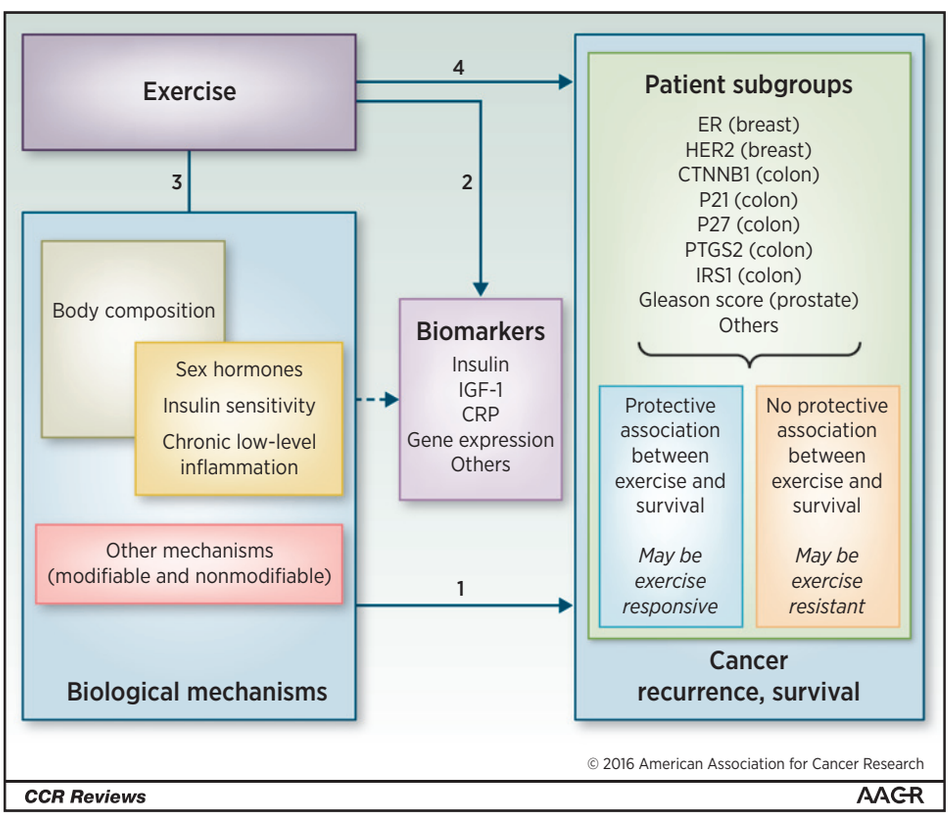

Figure 1.
Ways in which epidemiologic studies can inform precision exercise research. 1. observational studies relating biological mechanisms to cancer outcomes help demonstrate clinical relevance; 2. exercise trials showing exercise modes of action (and further defining the exercise prescription); 3. prior knowledge about exercise and biological mechanisms that can inform an exercise prescription and inform hypotheses about competing risks (e.g., diabetes); and 4. molecular epidemiology studies that generate hypotheses for preclinical testing and future efficacy trials and provide additional support for hypothesized biological mechanisms.

(e.g., leptin, adiponectin), insulin-like growth factors (e.g., IGF-1), pro- and anti-inflammatory markers (e.g., CRP, IL6, IL1ra), immune factors (e.g., natural killer cells), oxidative stress markers (e.g., urinary 8-oxo-dG), and prostate-specific antigen and testosterone in prostate cancer. Changes in angiogenic factors (56, 57), tumor gene expression (57), epigenetic mechanisms (58, 59), DNA damage, and telomerase activity (ClinicalTrials.gov Identifier: NCT02235051) were examined more recently. A benefit of exercise randomized controlled trials is their capacity to compare different types, frequencies, durations, and timing of exercise on cancer biomarkers, which can define an exercise prescription. Prior knowledge about exercise and the biological mechanisms underlying cancer survival (e.g., exercise for reducing body fatness or insulin resistance) can also inform a prescription. In addition, exercise can influence competing risks of diseases with shared mechanisms (e.g., diabetes), which, in turn, influence cancer outcomes (Fig. 1, #3). A limitation of biomarker randomized controlled trials is the inability to translate biomarker changes into cancer survival benefit, particularly for newly hypothesized or less reliable biomarkers.

Finally, as discussed above, molecular epidemiology studies can generate compelling hypotheses (Fig. 1, #4) to guide large-scale phase III trials incorporating precision exercise questions. These studies also support causality with respect to the hypothesized biological mechanisms (Fig. 1, #1). Hypotheses may also flow from primary prevention studies. For instance, ER/PR status (60), HER2 (61, 62), P53 (61), and *BRCA* mutation status (63) have been studied in relation to breast cancer risk, and CTNNB1 (64) and genetic variants in the IGF pathway (65) were examined in relation to colorectal cancer risk. Studies relating prediagnostic physical activity to survival are also informative. For example, interactions between prediagnosis physical activity and colorectal cancer survival with *BRAF* mutations, *KRAS* mutations, and MSI status were explored recently (66).

Conclusions

While much has been learned in exercise oncology, we are still at an early stage in the translational development pathway for precision exercise in cancer treatment. Epidemiologic research is still needed to assess the relationships between physical activity and cancer survival for additional cancer sites and using enhanced methods, although for colorectal and breast cancers, causality seems probable. The clearest need is for additional, large molecular epidemiology studies such as those that have emerged particularly in the past 5 years. The totality of this evidence will inform preclinical testing, preliminary safety, and efficacy trials, and ultimately, definitive clinical exercise trials with survival endpoints (5).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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