Chapter 3
Physical Activity and Cancer Survival

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Introduction

Current physical activity guidelines generated by the World Health Organization (WHO) recommend that the general population participate in at least 150 minutes of moderate aerobic physical activity per week (equivalent to 75 minutes of vigorous aerobic physical activity) in bouts of 10 minutes or more [1]. Guidelines for cancer survivors produced by the World Cancer Research Fund/American Institute for Cancer Research recommend that cancer survivors engage in regular physical activity following guidelines for the general population and further recommend that survivors should return to normal daily activities as soon as possible following diagnosis [2–4]. In 2018, the Clinical Oncology Society of Australia delivered a position statement on exercise in cancer care in which they recommend that exercise should be "embedded as part of standard practice in cancer care and to be viewed as an adjunct therapy that helps counteract the adverse effects of cancer and its treatment" [5]. This position statement raised some concerns in the exercise oncology community since the state of evidence regarding the feasibility, suitability, type, and dose of activity that should be recommended for all cancer patients and survivors remains unclear. Recognition exists, nonetheless,

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regarding the vital role that physical activity has during treatment, rehabilitation, and survival for cancer despite a lack of evidence in some areas. Furthermore, the field of precision medicine has also been applied to physical activity and cancer in a seminal paper led by Jones (2016) in which a framework for precision exercise oncology was provided [6]. In this chapter, we review the evidence on physical activity and survival in cancer populations while also providing insight into some elements of precision exercise oncology in efforts to discern which cancer patient and survivor groups could experience particular survival benefits with regular physical activity. The primary reviews of the evidence will focus on physical activity as it was reported in the included studies.

Physical Activity and Cancer Survival: Epidemiologic Research

The first study investigating the relationship between physical activity and survival outcomes in cancer survivors was published in 1992 [7]. However, this area of research did not garner much traction until 2005. Since then, there has been an exponential increase in the number of studies published evaluating the association between physical activity and mortality outcomes among cancer survivors. By 2019, identified through searches in PubMed, EMBASE, and SportDiscus, over 145 studies had been published on this topic. These studies provide sufficient data to permit the completion of meta-analyses that seek to quantify the direction and magnitude of association between physical activity and cancer survival.

The relationship between physical activity and survival outcomes following cancer has been most commonly investigated in breast [8–49], colorectal [8, 47, 48, 50–69], and prostate cancers [47, 48, 70–79] and all cancer sites combined [7, 8, 47, 48, 69, 79–117]. Nonetheless, in more recent years, findings from studies involving other single cancer sites, including bladder [79, 118], brain [79], childhood [119], esophagus [47, 79, 120, 121], female reproductive (endometrial, ovarian, and cervical) [47, 48, 79, 122–129], glioma [130], head and neck [47, 79], hematologic (leukemia, lymphoma, myeloma, and other hematopoietic cancers) [69, 79, 80, 131–134], kidney [79, 135], liver [8, 47], lung [8, 47, 69, 79, 80, 136, 137], melanoma [138], pancreatic [47, 69, 79, 80, 139–142], and stomach [47, 69, 79, 80, 120, 121] cancers, have also been published. Data collected for these analyses have most commonly been derived from prospective follow-up of cohorts of cancer cases identified either in case-control or cohort studies. There were also four randomized controlled exercise intervention trials that conducted long-term follow-up of trial participants for mortality outcomes [32, 33, 49, 132].

Summary of the Study Designs and Methods

Of the 145 studies published to date, cohorts from mostly developed countries have been investigated and include North America (Canada, Puerto Rico, and the USA), Europe

(Denmark, Finland, Germany, Italy, the Netherlands, Norway, Scotland, Sweden, Switzerland, the United Kingdom,) Australia/New Zealand, and Asia (China, Japan, Korea, Taiwan, Thailand, and Singapore). Contributing sample sizes varied widely, ranging from 103 to 1,290,000, as did the timing and method by which physical activity was assessed and reported before or after a cancer diagnosis. Only a few studies included repeated assessments that covered both pre- and post-diagnosis periods. The methods for assessing physical activity included self-administered physical activity questionnaires, interview-administered questionnaires, or direct measures of activity through accelerometers or exercise logs/diaries (used in the randomized controlled intervention trials); the majority relied on data from one of several self-administered physical activity questionnaires. In addition, 21 studies examined cardiorespiratory fitness (a potential surrogate measure of physical activity) and its association with cancer survival [7, 110, 114, 143–160]. The type of physical activity measured was primarily recreational activity or total physical activity, with a minority of studies assessing occupational and household activities as separate domains in addition to recreational activity. For most studies, the frequency, intensity, and duration of activities were assessed which permitted an estimation of the total energy expenditure in MET-hours/week. Overall, there is clear heterogeneity in the methods used for physical activity assessment, which needs to be considered when assessing findings derived from these studies.

Evidence Synthesis Methods

We used random effects DerSimonian and Laird models to assess the strength of the associations between physical activity and cancer survival for these studies. Specifically, we estimated the associations by time period of physical activity assessment (pre- or post-diagnosis) and by type of outcome (cancer-specific survival or all-cause mortality). For simplicity of presentation, and given the level of evidence for some cancer sites for which five or fewer studies have been published, we created five categories for the associations ranging from >20% statistically significant decreased mortality risks to >10% non-statistically significant increased risks. In addition, we examined each study to assess if the dose-response relationship between physical activity and mortality outcomes was investigated and if there was evidence of a statistically significant dose-response effect. We further reviewed the degree of consistency in the evidence across studies and categorized it as follows: (1) *yes* (with at least 10 different contributing estimates for which at least 75% had similar findings); (2) *moderate* (at least five contributing estimates with at least 75% demonstrating similar results or ≥ 10 estimates with 50–75% demonstrating similar findings); (3) *limited* (two to five contributing estimates with 75% displaying similar findings or more than five estimates with 50–75% showcasing similar findings); (4) or *no* (there was a lack of consistency (≤50% with similar findings) and/or too few estimates (i.e., only one contributing estimate) to determine consistency). These results were summarized for 18 cancer sites for which at least one study had been published that examined either pre- or post-diagnosis in association with either cancer-specific or all-cause mortality in cancer survivors (Table 3.1).

Table 3.1 Summary of the strength, dose-response, and consistency of the effects of pre- and post-diagnosis physical activity on all-cause or cancer-specific mortality outcomes by cancer site

Cancer Site	Timing of Physical Activity/Outcome	Number of studies	Strength of effect	Dose-response effect[a]	Consistency[b]
All cancers	Pre-dx: all-cause	1		0/0	No
	Post-dx: all-cause	6		2/2	Moderate
	Pre-dx: cancer-specific	33		13/17	Yes
	Post-dx: cancer-specific	4		2/2	Limited
Bladder	Pre-dx: cancer-specific	2		0/1	No
Brain	Pre-dx: cancer-specific	1		0/1	No
Breast	Pre-dx: all-cause	19		4/14	Yes
	Post-dx: all-cause	17		8/10	Yes
	Pre-dx: cancer-specific	23		0/18	Moderate
	Post-dx: cancer-specific	13		6/10	Yes
Childhood	Post-dx: all-cause	1		1/1	No
Colorectal	Pre-dx: all-cause	10		3/7	Yes
	Post-dx: all-cause	10		5/5	Yes
	Pre-dx: cancer-specific	14		3/12	Yes
	Post-dx: cancer-specific	6		4/4	Moderate
Esophagus	Pre-dx: all-cause	1		0/0	No
	Post-dx: all-cause	1		0/0	No
	Pre-dx: cancer-specific	2		0/2	Limited
Female Reproductive[c]	Pre-dx: all-cause	5		0/2	Moderate
	Post-dx: all-cause	4		0/1	Limited
	Pre-dx: cancer-specific	5		0/4	Limited
Glioma	Post-dx: all-cause	1		0/0	No
Head and Neck	Pre-dx: cancer-specific	2		0/2	No
Hematologic	Pre-dx: all-cause	3		4/6	Moderate
	Post-dx: all-cause	2		4/4	Moderate
	Pre-dx: cancer-specific	6		1/9	Yes
	Post-dx: cancer-specific	1		0/1	No
Kidney	Post-dx: all-cause	1		1/1	No
	Pre-dx: cancer-specific	2		1/2	No
	Post-dx: cancer-specific	1		0/1	No
Liver	Pre-dx: cancer-specific	3		3/4	Limited
Lung	Post-dx: all-cause	2		0/0	Limited
	Pre-dx: cancer-specific	5		4/6	Moderate
Melanoma	Pre-dx: all-cause	2		0/0	Limited
	Pre-dx: cancer-specific	1		0/0	No
Pancreas	Pre-dx: cancer-specific	8		0/10	No
Prostate	Pre-dx: all-cause	2		1/2	No
	Post-dx: all-cause	5		3/3	Moderate
	Pre-dx: cancer-specific	9		0/8	Moderate
	Post-dx: cancer-specific	4		2/3	Limited
Stomach	Pre-dx: all-cause	1		0/0	No
	Post-dx: all-cause	1		0/0	No
	Pre-dx: cancer-specific	4		2/5	Moderate

Colour Scheme	Strength of effect
	Statistically significant >20% decrease
	Statistically significant 0-20% decrease
	Non-statistically significant decrease >10%
	Null
	Non-statistically significant increase >10%

Abbreviations: *Pre-dx* pre-diagnosis, *Post-dx* post-diagnosis

[a]Dose-response: Number of estimates finding statistically significant dose-response ($p < 0.05$)/number of estimates evaluating dose-response

[b]Consistency: Established using the following criteria: (1) *yes* (with at least 10 different contributing estimates for which at least 75% had similar findings); (2) *moderate* (at least five contributing estimates with at least 75% demonstrating similar results or ≥10 estimates with 50–75% demonstrating similar findings); (3) *limited* (two to five contributing estimates with 75% displaying similar findings or more than five estimates with 50–75% showcasing similar findings); (4) or *no* (there was a lack of consistency (≤50% with similar findings) and/or too few estimates (i.e., only one contributing estimate) to determine consistency)

[c]Female reproductive cancers: Number of contributing estimates = pre-dx all-cause, endometrial ($n = 2$) and ovarian ($n = 3$); post-dx all-cause, endometrial ($n = 2$), ovarian ($n = 1$), and cervical ($n = 1$); pre-dx cancer-specific, endometrial ($n = 2$), ovarian ($n = 3$), and cervical ($n = 1$)

Overall Results

Findings presented in Table 3.1 support that the highest versus lowest levels of physical activity were associated with statistically significant decreases of >20% in cancer-specific or all-cause mortality outcomes in studies that assessed all cancer sites combined and ten other specific tumor sites, including breast, colorectal, female reproductive, glioma, hematologic, kidney, liver, lung, prostate, and stomach cancers. The strongest and most consistent evidence was observed for all cancer sites combined and breast, colorectal, and prostate cancers with data supporting an effect for all associations examined (i.e., pre- and post-diagnosis physical activity and cancer-specific and all-cause mortality).

We also examined the question of timing of physical activity in relation to mortality outcomes (Figs. 3.1, 3.2, 3.3, 3.4, 3.5, and 3.6). When all cancer sites combined,

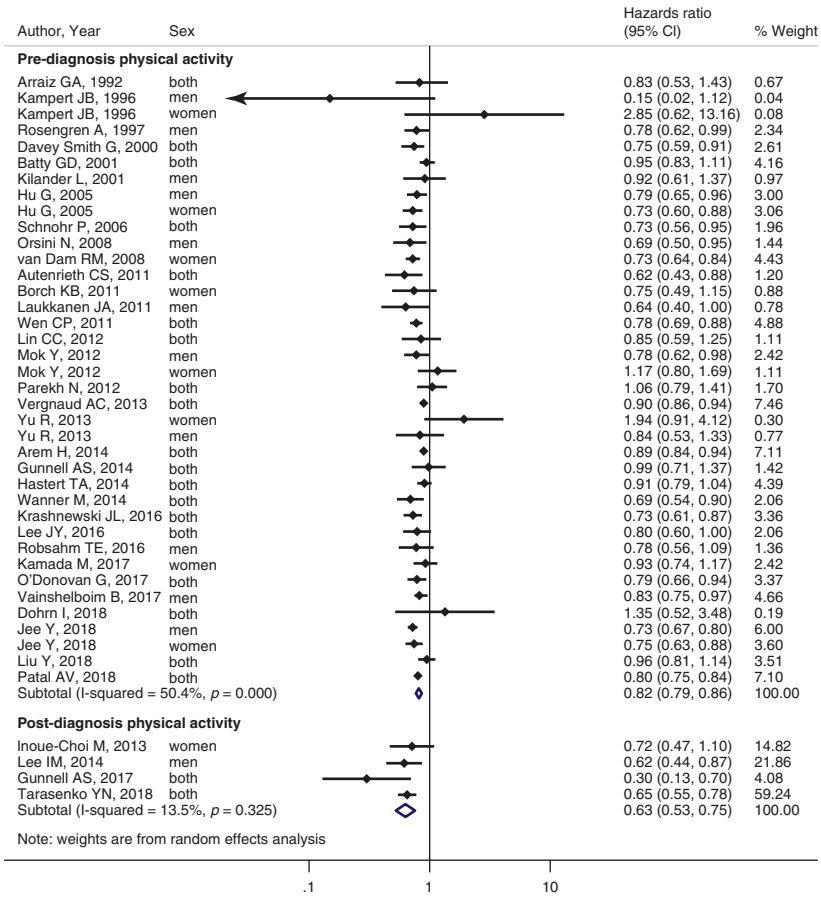

Fig. 3.1 Pre- and post-diagnosis physical activity and cancer-specific mortality for studies that combined all cancer sites

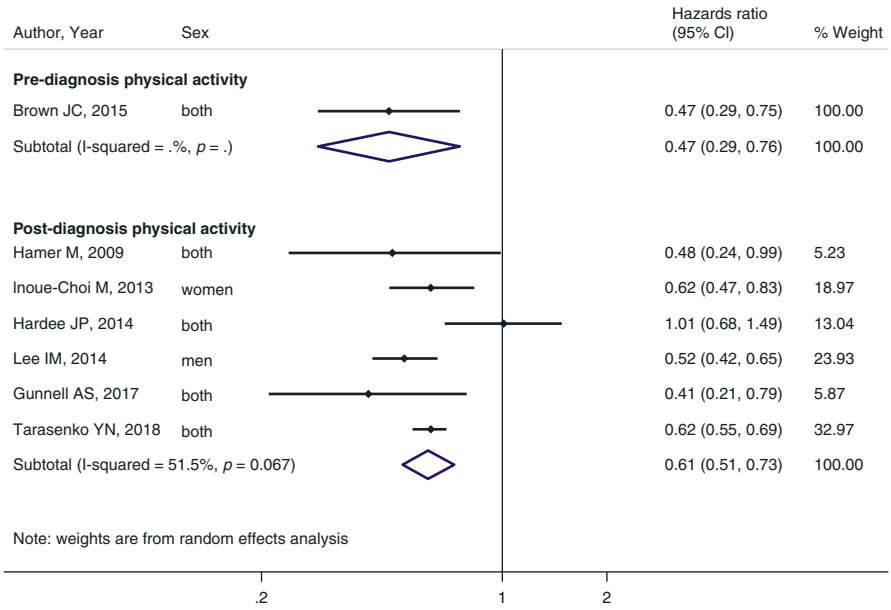

Fig. 3.2 Pre- and post-diagnosis physical activity and all-cause mortality for studies that combined all cancer sites

breast and colorectal cancers were considered, reductions in mortality risks were observed for both pre- and post-diagnosis activity. However, post-diagnosis physical activity was generally more protective (HR ~0.60) compared with pre-diagnosis physical activity (HR ~0.80) for both cancer-specific and all-cause mortality estimates.

Population Subgroups: Effects by Race

The emerging area of precision oncology has raised interest in determining whether patient sociodemographic characteristics or clinical and pathologic characteristics might predict populations or subgroups within a specific cancer population that could particularly benefit from physical activity. Unfortunately, to date, there exist only a limited number of studies available to contribute to meta-analyses that seek to evaluate the relationships between subgroups within a study population and physical activity. While this lack of evidence adversely influences the strength of statements that can be drawn from our findings, several noteworthy findings are worth consideration. First, breast cancer is the only cancer site to have investigations completed on racial subgroups [17, 23, 38, 39]. Yet the established survival disparities by race for most cancers highlight the importance of determining whether or not race is a potential effect modifier of the association between physical activity and cancer survival. Furthermore, physical activity levels and types of physical activity undertaken

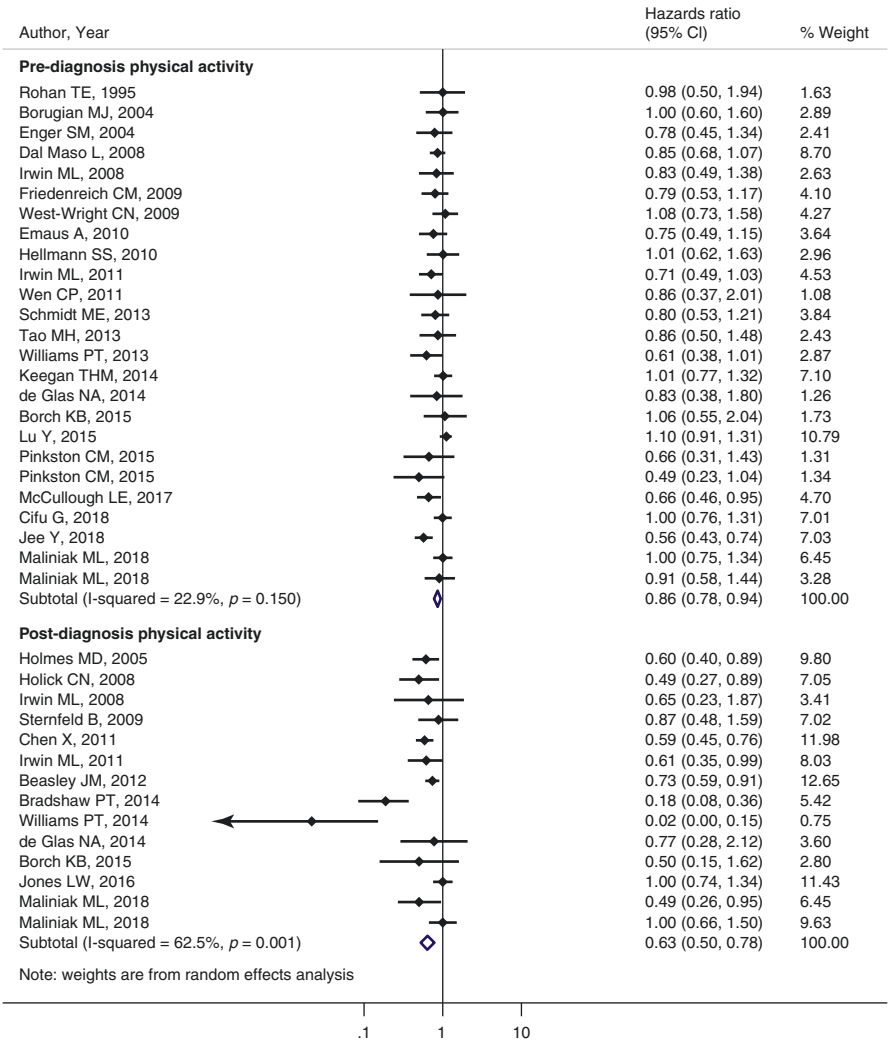

Fig. 3.3 Pre- and post-diagnosis physical activity and breast cancer–specific mortality

have been shown to differ by race. For example, African-American women are less likely to meet physical activity guidelines compared with white women; Hispanic women most frequently report walking and household activities, while non-Hispanic white women are more likely to report participation in sport-based activities [161]. Preliminary findings from our meta-analyses, using data from the few breast cancer studies that provided race-specific estimates, suggest that physical activity (pre- and post-diagnosis) is at least as beneficial for breast cancer-specific and all-cause mortality for African-American, Hispanic, and Asian-American women, as it is for white women. More data within and beyond breast cancer cohorts are required to improve the consistency and strength of these findings.

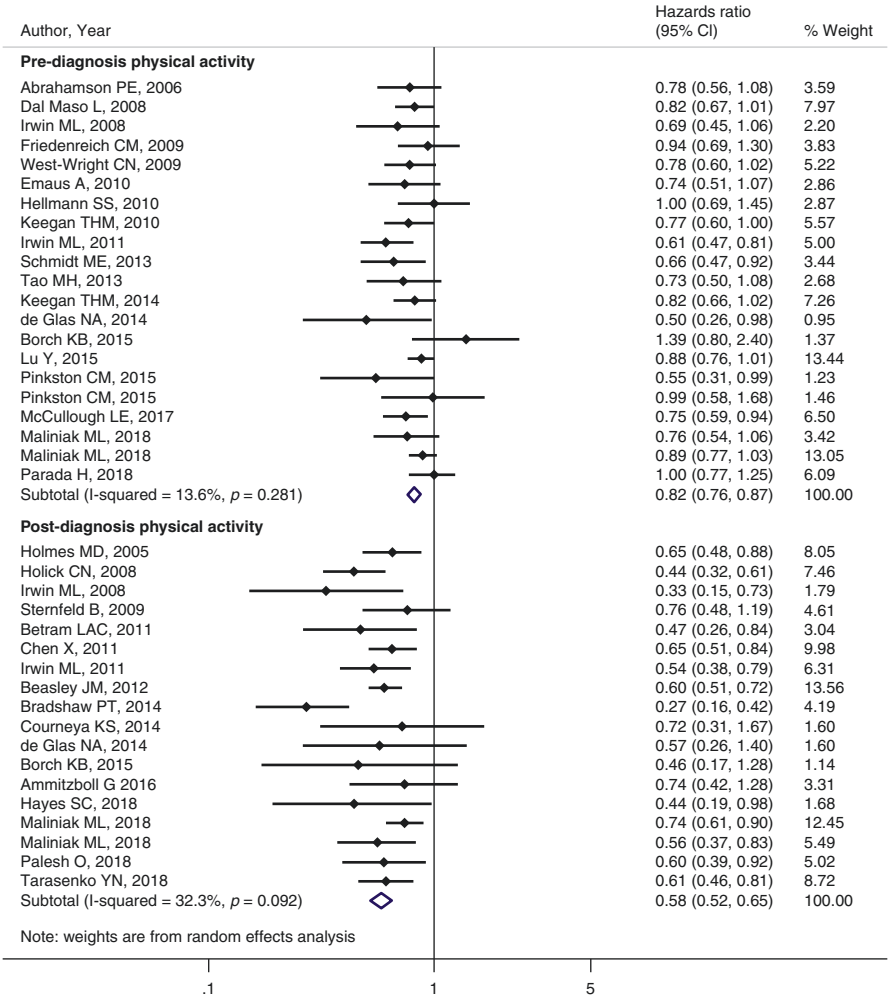

Fig. 3.4 Pre- and post-diagnosis physical activity and all-cause mortality in breast cancer survivors

Precision Oncology: Effects by Hormone Receptor Status

The differences in etiology, treatment, and prognosis for hormone receptor-positive and hormone receptor-negative cancers have also raised questions regarding the potential effect of physical activity in providing survival benefits among these subgroups [162]. Nine studies, involving women with breast cancer, presented stratified estimates for effect of physical activity by hormone receptor status [9, 13, 17, 20, 25, 29, 31, 38, 41], enabling us to explore these relationships in meta-analyses. We found statistically significant reductions of risk for both hormone receptor-positive and hormone receptor-negative breast cancers associated with

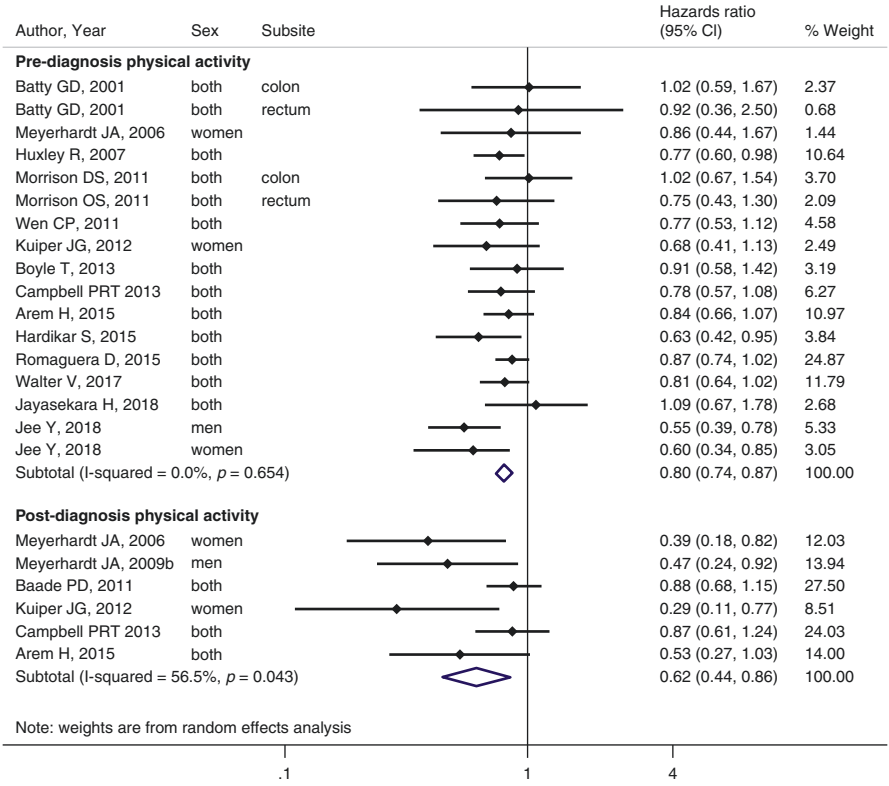

Fig. 3.5 Pre- and post-diagnosis physical activity and colorectal cancer-specific mortality

post-diagnosis physical activity and both cancer-specific and all-cause mortality outcomes (cancer-specific HR+ 0.58 (0.45–0.75), HR− 0.59 (0.42–0.83); all-cause HR+ 0.66 (0.51–0.84), HR− 0.57 (0.42–0.78)). Hence, physical activity seems to confer survival benefits regardless of hormone receptor status in breast cancer survivors. To date, there are an insufficient number of studies examining triple-negative breast cancers in association with physical activity and survival to draw any conclusions for this patient population.

Precision Oncology: Effects by Cancer Stage

Another important predictor of survival after cancer is stage at diagnosis. As such, we examined the results from studies with data stratified by stage (Fig. 3.7), with studies involving colorectal and breast cancers providing sufficient data for this analysis. No clear patterns were identified for the association between physical activity and survival. Overall, there was evidence of a risk reduction of mortality outcomes for all cancer stages, with one notable exception. Specifically, findings

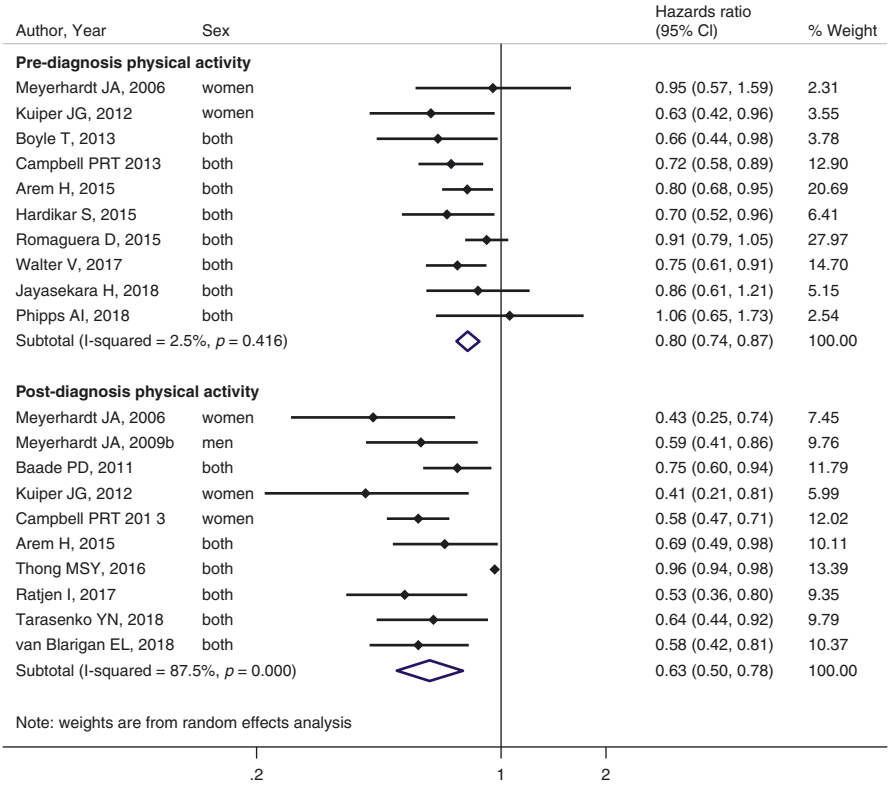

Fig. 3.6 Pre- and post-diagnosis physical activity and all-cause mortality in colorectal cancer survivors

from one colorectal cancer study with estimates for patients with stage IV disease suggested that post-diagnosis physical activity was associated with an increased risk of mortality, though this estimate should be interpreted with caution because of its small sample size and consequently wide confidence intervals.

Other important population subgroups warranting attention in future research include differences by sociodemographic characteristics and clinicopathologic characteristics, such as molecular tumor markers. To date, there have been an insufficient number of studies conducted on these population subgroups to provide any summaries.

Other Cancer Survival Outcomes and Physical Activity

While cancer-specific and all-cause mortality outcomes are the most commonly reported outcomes to consider, other survival outcomes have been investigated. For cancer recurrence or progressions, the following outcomes have been assessed: first recurrence or progression, late recurrence (>5 years), non-relapse mortality,

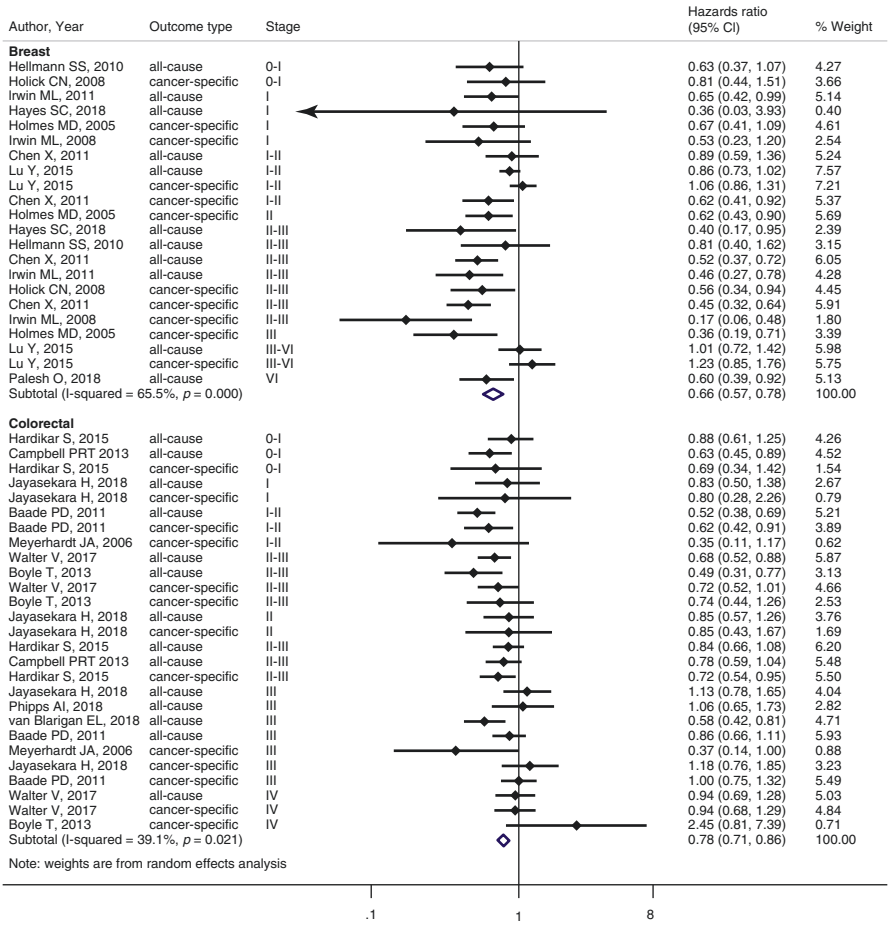

Fig. 3.7 Physical activity and all-cause and cancer-specific mortality in breast and colorectal cancer, by stage

progression-free survival, recurrence, recurrence-free interval, recurrence-free survival, progression or new primary cancer, recurrence-free period, recurrent/progressive primary cancer, relapse/disease-specific mortality, and time to recurrence. Unfortunately, the inconsistency in the definitions of these additional survival outcomes made it particularly challenging to compare findings within and between cancer sites. Acknowledging these limitations, by combining categories of first recurrence or progression, recurrence, progression or new primary cancer, and recurrent/progressive primary cancer, we found seven studies investigating the effects of physical activity (either pre- or post-diagnosis) on specifically first recurrence or progression in breast cancer [9, 13, 18, 19, 24, 28, 41], one in prostate cancer [76], and one in childhood cancers [119]. The pooled hazards ratios for each of these cancer sites are 0.90 (0.78–1.04), 1.05 (0.80–1.39), and 0.83 (0.59–1.17),

respectively. While the lack of statistical significance in these findings, alongside potential heterogeneity in the outcome measures, highlights the need for caution in interpreting these findings, it seems plausible that a trend toward a potentially protective effect of physical activity is emerging, at least in relation to breast cancer recurrence/progression. The use of standardized endpoint definitions, such as those provided by the STEEP guidelines, in future observational epidemiologic studies would facilitate future and important summaries [163].

Change in Physical Activity and Cancer Outcomes

Following a diagnosis of cancer, patients are often motivated to seek out and implement positive changes to their behavior, for multiple reasons, which include to improve coping, rehabilitation, quality of life, and survival [164]. From a public health and patient perspective, it would be particularly useful to understand whether or not changes in physical activity from pre- to post-diagnosis also influence survival. We found nine studies that reported on the relationship between physical activity changes and cancer-specific or all-cause mortality in cancer survivors, with either "unchanged levels" or "inactive" defined as the reference category for comparisons across subgroups [17, 26, 50, 53, 74, 76, 126, 134, 135]. Overall, increasing physical activity from pre- to post-diagnosis levels was associated with decreased risk of mortality (HR, 0.79, 0.69–0.92). When stratified by type of survival outcome (all-cause and cancer-specific mortality), results remained relatively unchanged for all-cause mortality (HR, 0.76, 0.64–0.90), but the magnitude of effect was attenuated, and the estimate was no longer statistically significant for cancer-specific survival (HR, 0.84, 0.65–1.08) (Fig. 3.8). These results indicate that increasing physical activity levels post-diagnosis, irrespective of meeting levels consistent with physical activity guidelines, may have positive effects on survival. However, the heterogeneity which exists relating to the method of determining physical activity changes (including differences in what constitutes a change and timing of the change) highlights the need for caution in interpreting statistical significance and clinical relevance of findings, as well as the need for more research in this area.

Resistance Training and Cancer Survival

The studies included in this review have primarily examined the effects of aerobic physical activity or total physical activity on survival outcomes in cancer populations. Despite the more recent inclusion of resistance exercise in physical activity guidelines for people with cancer [1], there is limited information pertaining to the effect of resistance training, or muscle-strengthening activity, on survival outcomes in cancer populations. Specifically, six studies identified in our review assessed this association in populations consisting of all cancer survivors, as well

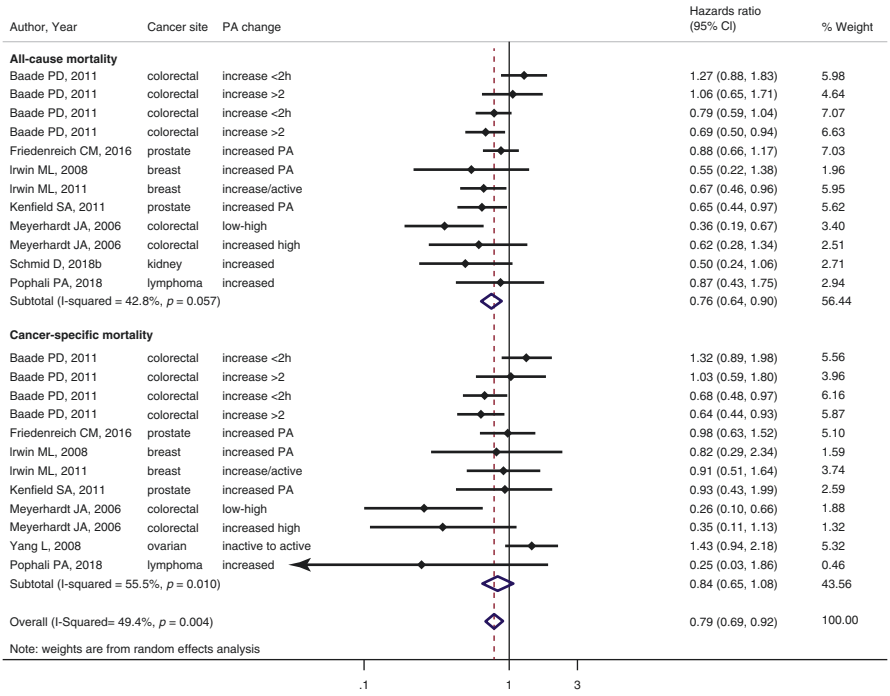

Fig. 3.8 Forest plot of increases of physical activity from pre- to post-diagnosis related to all-cause and cancer-specific mortality

as independently for colorectal, breast, endometrial, and prostate cancer survivors (Table 3.2) [48, 56, 100, 102, 108, 112]. These studies varied in their definitions of participation in muscle-strengthening activities from assessing lifetime resistance training as a dichotomous variable of yes versus no to assessing if participants met the strength training guidelines. Overall, while there was a trend, based on effect size for decreases in both all-cause and cancer-specific mortality outcomes, for cancer survivors who reported engaging in the highest versus lowest categories of strength training (HR range, 0.46–1.15), however, confidence intervals often crossed the null value. Of particular note are findings derived from a cancer cohort study that compared individuals who met neither aerobic nor muscle-strengthening guidelines to individuals who met either one or both guidelines [48]. Results suggested that meeting both strength training and aerobic activity guidelines had a compounding effect, wherein stronger improvements in survival were observed when both components of physical activity guidelines are met, compared to when only one component of guidelines is met. These represent important findings, particularly relevant to physical activity guidelines promoted to those with cancer, but also require confirmation in future epidemiological and clinical trial research. Since there is currently only one study that we identified which investigated the compounded effect of meeting both aerobic and strength training physical activity guidelines, future

Table 3.2 Summary of six studies investigating the effect of muscle-strengthening exercises on mortality outcomes in cancer survivors

First author, year, country	Study name/ description	Sample size	Cancer type	Muscle-strengthening definition	Results
Boyle et al. 2013, Australia [56]	The Western Australia Bowel Health Study	879	Colorectal cancer	Lifetime resistance training (definite vs. none) based on the name of activities listed on physical activity questionnaire	*All-cause mortality* Males: HR 0.64 (0.26–1.60) Females: HR 0.46 (0.13–1.66) *Cancer-specific mortality* Males: HR 0.81 (0.32–2.05) Females: HR 0.50 (0.14–1.84)
Yu et al. 2013, China [100]	Community-dwelling Chinese men and women aged 65 and older	2867	All cancers	The Physical Activity Scale of the Elderly (PASE). Strenuous/muscle-conditioning activity, active vs. inactive	*Cancer-specific mortality* Males: HR 0.89 (0.57–1.39) Females: HR 1.15 (0.59–2.25)
Hardee et al. 2014, USA [102]	The Aerobics Center Longitudinal Study	2863	All cancers	Participants who responded "yes" to free weights or weight training and had exercised at least 1 day per week vs. those who did not	*All-cause mortality* HR 0.67 (0.45–0.99)
Kraschnewski et al. 2016, USA [108]	The 1997–2001 National Health Interview Survey (NHIS)	30,162	All cancers	Participants responded how often they partook in leisure-time physical activities specifically designed to strengthen muscles. Categorized into whether guidelines of at least twice per week were met vs. not	*Cancer-specific mortality* HR 0.81 (0.69–0.96)
Kamada et al. 2017, USA [112]	The Women's Health Study	28,879	All cancers	Participants asked what their approximate time spent per week on weight lifting/ strength training. ≥60 minutes/week vs. 0 minutes/week	*Cancer-specific mortality* HR 0.92 (0.68–1.24)

(continued)

Table 3.2 (continued)

First author, year, country	Study name/ description	Sample size	Cancer type	Muscle-strengthening definition	Results
Tarasenko et al. 2018, USA [48]	The 1999–2009 National Health Interview Survey	13,997	All cancers and separately by breast, prostate, colorectal, and endometrial cancers	Whether participants met aerobic (≥150 minutes/week) or strength training (≥2 days per week) guidelines. Met guidelines on muscle-strengthening activities only or met both guidelines vs. met neither guidelines	*All-cause mortality: All cancers* Only muscle: HR 0.94 (0.78–1.14) Both: HR 0.60 (0.50–0.73) *Cancer-specific mortality: All cancers* Only muscle: HR 0.89 (0.63–1.25) Both: HR 0.52 (0.38–0.72) *All-cause mortality: Breast* Only muscle: HR 0.90 (0.58–1.39) Both: HR 0.72 (0.45–1.17) *All-cause mortality: Prostate* Only muscle: HR 0.96 (0.65–1.40) Both: HR 0.54 (0.34–0.86) *All-cause mortality: Colorectal* Only muscle: HR 0.87 (0.50–1.53) Both: HR 0.80 (0.39–1.66) *All-cause mortality: Endometrial* Only muscle: HR 0.48 (0.20–1.16) Both: HR 0.92 (0.40–2.10)

research is warranted to determine whether or not these findings are observed by others. Mechanistically, there is biologic plausibility for an association between strength training and improved survival. Strength training is more effective than aerobic exercise at leading to increases or preservation over time in muscle mass and strength, higher muscle mass and strength are associated with improved physical functioning and quality of life, and higher muscle mass and strength have independently been associated with improved survival [165].

Cardiorespiratory Fitness and Cancer Survival

Cardiorespiratory fitness (CRF), also known as exercise tolerance or physical fitness, refers to the ability of the circulatory, respiratory, and musculoskeletal systems to supply oxygen during sustained physical activity [166]. While higher physical activity levels have been associated with higher physical fitness, these terms are not synonymous, and it is possible that an individual may report high levels of physical activity but have low physical fitness. Consequently, exploring the relationship between physical fitness and survival outcomes following cancer is relevant. Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure [167, 168]. In contrast, physical fitness (as captured by CRF) represents the capacity to which an individual is able to achieve or perform physical activity [168]. With these distinctions made, it is important to also investigate the utility of using cardiorespiratory fitness as a predictor of cancer survival.

Schmid and Leitzmann completed a systematic review and meta-analysis on this topic in 2015 [169], which identified six studies capturing physical fitness information on 71,654 individuals and 2002 cases of total cancer mortality [7, 143–147]. From this review, these authors found that compared to low levels of cardiorespiratory fitness, intermediate levels and high levels of cardiorespiratory fitness were associated with statistically significant decreased risks of total cancer mortality (relative risks, 0.80 [0.67–0.97] and 0.55 [0.47–0.65], respectively). Several studies were not included in their review that examined total cancer mortality and cardiorespiratory fitness [110, 114, 148–155], and since publication of their review, there have been additional studies reporting on the relationship between cardiorespiratory fitness and site-specific cancer mortality [156–160]. These additional articles support and strengthen Schmid and Leitzmann's findings with growing evidence to suggest that intermediate and high levels of cardiorespiratory fitness compared to low levels of cardiorespiratory fitness are associated with survival benefits in cancer populations.

There are some limitations to this body of research, including that the majority of studies have been restricted to male samples [110, 114, 147, 149, 150, 152, 153, 155–158, 160] and that a high proportion of the published findings have used data from the Aerobics Center Longitudinal Study [153, 155, 157–160], both of which limit the generalizability of results to the wider cancer population. With these

caveats taken into consideration, the evidence does suggest that, overall, there are inverse and statistically significant associations between cardiorespiratory fitness and improved survival outcomes in cancer populations.

Exercise and Cancer Survival: Evidence from Clinical Trials Research

Besides the observational epidemiologic studies reviewed thus far, preliminary clinical trial evidence on the potential effect of participation in an exercise intervention, during or following treatment for cancer, on survival outcomes is also emerging. Data derived for these analyses have come from cohorts with breast cancer [32, 49], lymphoma, and leukemia [132, 170] and patients with bone metastasis following a range of cancers [171] (sample size range across the five trials, 60–337), with >65% of participants in all studies having completed or currently receiving chemotherapy during the intervention period. Interventions evaluated have involved aerobic-based only, resistance-based only, and aerobic- and resistance-based exercise, commencing during or post-active adjuvant therapy, with varying durations (range, 12–32 weeks) and mixed degree of supervision. Due to the small number of trials, and degree of heterogeneity between the samples and interventions evaluated, we provide here a narrative summary of the findings (rather than results from meta-analyses). A beneficial effect of exercise on all-cause mortality (HR, 0.45–0.71) was found in three of the five trials, with results remaining relatively unchanged following adjustment for other prognostic characteristics [32, 49, 132]. However, no effect of exercise on all-cause mortality (HR, 1.06 and 1.10) was reported in the remaining two trials (involving patients with metastatic disease and patients with lymphoma) [170, 171].

Comparison of findings from the two breast cancer trials warrants particular attention [32, 49]. First, sample characteristics, including age, body mass index, and stage of disease, were relatively similar between the two trials. In addition, of the five trials published to date on this topic, these two trials had the largest sample sizes (242 [32] and 337 [49]), evaluated the longest intervention (approximately 17 weeks in one trial [32] and 32 weeks for the other [49]), and longest time to follow up of survival data (89 [32] and 100 months [49]), minimizing some of the heterogeneity that would limit comparisons of findings. Further, the findings derived from these two trials for the effect of exercise on improving overall survival and disease-free survival were remarkably similar (HRs for overall survival, 0.60 [32] and 0.45 [49]; HRs for disease-free survival, 0.68 [32] and 0.66 [49]). Finally, despite the exploratory nature of the analyses undertaken (with limited power), the effect sizes observed are consistent with those observed in observational breast cancer studies, which suggest that improvements in survival of greater than 20% can be accrued through participation in physical activity post-diagnosis. These exciting, albeit preliminary, findings suggest that influencing physical activity behavior through exercise intervention may be beneficial for cancer outcomes.

Ongoing and Future Research

There is now not only a clear need for investigating causal associations between physical activity and cancer survival in adequately powered, randomized controlled trials but also the necessary evidence to support trial design, implementation, and evaluation. In addition, the recognized limitations in previous observational epidemiologic studies need to be addressed in future cohort studies. Progress in science addressing this gap is already happening. For example, the Alberta Moving Beyond Breast Cancer (AMBER) cohort study involves objective assessment of physical activity, sedentary behavior, health-related fitness, and breast cancer outcomes (target sample size, 1500) [172]. These design features address limitations of existing cohort studies evaluating physical activity and cancer survival outcomes, which have relied heavily on self-reported assessments of dose and type of physical activity, without concurrent assessment of fitness and sedentary behavior. Further, there now exist at least four randomized controlled exercise intervention trials, with target sample sizes providing adequate power for survival analyses following colon, metastatic prostate, ovarian, and allogeneic hematopoietic stem cell transplant patients [173–176]. Together these studies provide the ideal platform for improvements in knowledge needed to transform cancer care practice. Current and future research that seeks to explore optimal exercise dosage, modes of delivery, timing and duration of interventions, and characteristics that influence ability and capacity for a physiological and psychological response to exercise will ensure the workforce is equipped to prescribe evidence-based exercise to the growing cancer survivorship population.

Summary

Rapidly accumulating evidence from observational epidemiologic studies and follow-ups from randomized controlled exercise intervention trials supports recommendations to maintain and increase physical activity after cancer diagnosis for improved survival outcomes. This review found evidence for improved cancer-specific and all-cause mortality outcomes for 11 different cancer sites (10 specific cancer sites and all cancer sites combined), as well as preliminary evidence for decreased risk of recurrence and progressions. Increasing activity from pre- to post-diagnosis may also improve these outcomes after cancer. Population subgroups that might most benefit from physical activity remain unclear given the paucity of evidence to date. All stages of cancer appear to benefit equally from physical activity done either before or after cancer. More research is needed that focuses on these subgroups defined by sociodemographic characteristics as well as clinical and pathologic tumor characteristics. Additional research also needs to clarify the appropriate type, dose, and timing of physical activity that are most beneficial for improved survival outcomes by cancer site. This future research will help address the remaining gaps in understanding on the appropriate physical activity recommendations that can be provided to improve survival after cancer.

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