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Meta-Analysis

META-ANALYSIS

Physical Activity and Mortality in Cancer Survivors: A Systematic Review and Meta-Analysis

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Abstract

Background: Recommendations for improved survival after cancer through physical activity (PA) exist, although the evidence is still emerging. Our primary objective was to conduct a systematic review and meta-analysis of the association between prediagnosis and postdiagnosis PA and survival (cancer-specific, all-cause, and cardiovascular disease mortality) for all cancers and by tumor site. Secondary objectives were to examine the associations within population subgroups, by PA domain, and to determine the optimal dose of PA related to survival.
Methods: PubMed, EMBASE, and SportsDiscus databases were searched from inception to November 1, 2018. DerSimonian-Laird random-effects models were used to estimate the summary hazard ratios (HRs) and 95% confidence intervals (CI) for primary and secondary analyses and to conduct dose-response analyses.
Results: Evidence from 136 studies showed improved survival outcomes with highest vs lowest levels of prediagnosis or postdiagnosis total or recreational PA for all-cancers combined (cancer specific mortality: HR = 0.82, 95% CI = 0.79 to 0.86, and HR = 0.63, 95% CI = 0.53 to 0.75, respectively) as well as for 11 specific cancer sites. For breast and colorectal cancers, greater reductions were observed for postdiagnosis PA (HR = 0.58–0.63) compared with prediagnosis PA (HR = 0.80–0.86) for cancer-specific and all-cause mortality. Survival benefits through PA were observed in most subgroups (within sex, body mass index, menopausal status, colorectal subtypes, and PA domain) examined. Inverse dose-response relationships between PA and breast cancer-specific and all-cause mortality were observed, with steep reductions in hazards to 10–15 metabolic equivalent hours per week.
Conclusion: Higher prediagnosis and postdiagnosis levels of PA were associated with improved survival outcomes for at least 11 cancer types, providing support for global promotion of PA guidelines following cancer.

The role of physical activity (PA) in cancer prevention is well recognized, with recent publications by the World Cancer Research Fund/American Institute for Cancer Research (1) and the 2018 Physical Activity Guidelines for Americans Report highlighting its importance to global health (2). Since the mid-2000s, there has been an exponential increase in studies evaluating the link between PA and survival outcomes that has resulted in some reviews on this topic (3). Although published reviews have explored the relationship between PA and survival (cancer-specific or all-cause mortality) following breast (4–9), colorectal (6,10), or all cancer (11,12), to date there have been no systematic reviews and meta-analyses examining *all* available cancer sites (including all-cancer as well as specific cancer sites) with cancer-specific and all-cause mortality outcomes. In addition, cardiovascular disease (CVD) is receiving increasing research attention as a leading cause of mortality for those with cancer. Yet, despite the known benefits through PA on CVD risk and survival, there are no available reviews evaluating cardiovascular mortality following any cancer.

In part, as a consequence of the exponential growth in PA and cancer survival epidemiological research, the momentum behind endorsing and promoting PA in the prevention and management of cancer has also grown (13). Concurrently, however, concerns have been raised about whether there is

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sufficient evidence to support the benefits of PA participation for all people with cancer or, alternatively, whether the evidence supports benefit through PA only for specific cancer types or subgroups within cancer types (that is, is dependent on sex, body mass index (BMI), menopausal status, or subtypes within a specific cancer). In addition, the extent to which the evidence can guide recommendations around PA domain (ie, total, recreational [leisure time], occupational, household) and dose of PA and for whom is unclear (14). Hence, there is a need for rigorous review of the rapidly evolving evidence base. As such, the primary objective of this systematic review and meta-analysis was to evaluate the association between prediagnosis and postdiagnosis PA and survival (primary outcomes: cancer-specific mortality, all-cause mortality, and CVD mortality) for all cancer and by specific cancer sites by using data from all available observational epidemiologic studies and randomized, controlled trials. Secondary objectives included assessing these associations by sex, BMI, menopausal status, and colorectal cancer subtype; evaluating the associations between different domains of PA (ie, total, recreational [leisure time], occupational, household) and survival outcomes; and determining the dose-response relationship between PA and cancer survival.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (15). Additionally, the protocol was registered in PROSPERO (registration number: CRD42018103290).

Literature Search Strategy

PubMed, EMBASE, and SportDiscus were searched from inception to July 5, 2018, using the search strategy "(physical activity OR motor activity OR exercise) AND (cancer OR neoplasm* OR carcinoma OR adenocarcinoma OR sarcoma OR tumor) AND (mortality OR recurrence OR progression OR outcome* OR survival) AND (survivors OR survivor OR survivorship OR patients OR patient)." Keywords (including any associated synonyms) along with medical subject headings for PA, cancer, and mortality were included. There were no restrictions by date, language, or geographical region. Reference lists of all included studies and relevant review articles were searched manually to identify additional studies, and e-alert notifications in PubMed captured additional articles through November 1, 2018.

Eligibility Screening

Eligibility was assessed independently and in duplicate using a two-stage process. First, two independent reviewers (CRS and ML, acknowledgments) screened title and abstracts of all captured literature. Studies were considered for full-text review if the title or abstract indicated that the exposure was PA and the outcome was related to survival outcomes following cancer (survival, mortality, recurrence, progression, etc) in human populations. If relevance was uncertain, the study was carried forward for full-text review. Second, two independent reviewers (CRS and either RKP, NM, or RU, acknowledgments) reviewed the remaining studies in their entirety. Inclusion criteria for full-text review were as follows: 1) the original peer-reviewed published research was available; 2) the exposure was PA, presented with a comparator group (ie, not continuously); 3) one or more mortality outcomes were reported (ie, cancer-specific mortality, all-cause mortality in cancer patients, CVD mortality in cancer patients); 4) the outcomes reported included a point estimate of risk, hazards, or odds ratios; 5) the study design was observational cohort or randomized trial (case reports and reviews were excluded).

Agreement between the two reviewers was quantified at the full-text review stage using percentage agreement and kappa statistics. Disagreements were resolved by consensus-based discussion between reviewers. In the event that there were multiple publications describing the same population with the same domain of PA exposure and mortality outcome, with no new subgroups of interest presented, the article presenting the largest sample size was retained in the review.

Data Extraction

A data collection form, developed specifically for this review, was used to extract and record author, publication year, study name, location, sample size, number of deaths, recruitment years, date of last follow-up, follow-up period, method of PA assessment, and outcome ascertainment source from eligible publications. We additionally extracted the following variables: cancer type, outcome type, timing of PA, domain of PA, high and low activity categories, activity units, hazard estimates and 95% confidence intervals for the highest vs lowest category of PA from the most adjusted model, population subgroups data on sex, BMI (kg/m^2), menopausal status, and estimates by colorectal cancer subsite and by domain of PA. We calculated the reciprocal of the reported point estimate if the lowest vs the highest level of PA was presented. When "floating" confidence intervals were reported, we converted them to conventional confidence intervals with a reference category (16). We contacted six authors (regarding eight papers) via e-mail up to two times to request information that was essential for meta-analysis; four authors replied.

Decision rules for data extraction were established to align with our primary aim and ensure consistent extraction of the exposure of interest: physical activity. For example, if multiple estimates were presented for different activity intensities, we extracted, in priority order, the point estimate for all intensities, moderately vigorous, vigorous, moderate, and finally light intensities. If multiple domains of PA were reported, we extracted, in priority order, the point estimate for total, recreational, occupational, and finally, household PA. If multiple estimates were presented for different life-periods prediagnosis, we extracted the estimate closest to diagnosis, rather than lifetime PA, to capture the short-term effects of exercise. Finally, if multiple estimates were provided for different units of activity, we extracted, in hierarchical order, the following: metabolic equivalent duration (MET; one MET is considered to be the resting metabolic rate achieved during quiet sitting [17]), hours per week, energy expenditure (kilocalories or kilojoules), frequency (times per day), and ordinal or rank (ie, scale of 1–10, categories).

Study Quality Assessment

A single reviewer (CRS) used the Newcastle-Ottawa Scale to assess the quality of each included study (18). This scale assesses the quality of included studies with scores ranging from zero (indicating poor-quality studies) to nine (indicating high-quality studies). The scores come from three domains: selection,

comparability, and outcome. The domain of selection was worth a maximum of four points based on sample selection (two points if the sample was representative of the exposed cohort and one point if the sample was composed of a selected group of individuals, ie, nurses, volunteers); ascertainment of exposure (one point if PA was ascertained through interview or actigraphy and zero points if self-administered); and outcome (one point if outcome was not present at start of study). The domain of comparability was worth a maximum of two points, with one point being awarded if models controlled for age, and an additional point awarded if models controlled for additional confounders. Finally, the domain of outcome was worth a maximum of three points based on outcome assessment (one point if outcome was obtained through record linkage), length of follow-up (one point if study had a follow-up time of more than three years), and loss to follow-up (one point if loss to follow-up was described, or if study had complete follow-up).

Statistical Analysis

To account for heterogeneity within the included studies, estimates were combined only if they pertained to the same cancer type, outcome type (cancer-specific, all-cause, or CVD-specific mortality), and timing of PA (prediagnosis or postdiagnosis). To account further for the inherent between-study heterogeneity in the population of patients, we used DerSimonian and Laird random-effects models to derive summary estimates of hazards depicted graphically with forest plots (19). Studies were represented once per meta-analysis except when results were only available for subgroup (ie, by sex). In these instances, each subgroup was treated as an independent study within random-effects models to acknowledge clinical heterogeneity and to reduce within-study confounding. Meta-regression and stratified analyses were performed to ensure that summary estimates did not differ by time-scale (ie, healthy cohorts vs cancer survivor cohorts) (20). Sensitivity analyses were performed, removing each study one by one to examine the impact of combining randomized, controlled trials with observational studies. Subgroup meta-analyses were conducted across strata of cancer type, outcome type, and timing of PA by domain of PA (total, recreational and/or leisure time, transportation, occupational, household), BMI ($<25\,kg/m^2$, $\geq 25\,kg/m^2$), sex (male, female), menopausal status (premenopausal, postmenopausal; where studies presented results by age, we used a cut point of 55 years whereby younger than 55 years was classified as premenopausal and older than 55 years was classified as postmenopausal; limited to breast cancer), and colorectal cancer subsite (colon, rectum). Where there were sufficient studies presenting estimates based on recreational PA volume in MET hours per week, we performed random-effects dose-response analyses (21). We applied the midpoint of each exposure category or the limit for open-ended exposure categories (eg, 10–20 was assigned a value of 15; <3 was assigned a value of 1.5).

Heterogeneity was assessed using I^2 statistics, which serve to describe the percentage of variation across studies due to heterogeneity rather than chance; I^2 values of 25%, 50%, and 75% indicate low, moderate, and high levels of heterogeneity, respectively (22). Publication bias was assessed pertaining to our primary objective with three or more estimates qualitatively through visual inspection of funnel plots and quantitatively using the Begg rank correlation test and Egger regression test for funnel plot asymmetry (23,24). All analyses were conducted using Stata software (version 15.1; StataCorp LP, College Station, TX); *P* values less than .05 were considered to be statistically significant and all tests were two-sided.

Results

Literature Search

We identified 15 760 records from our database search, five from PubMed e-alerts, and 31 through other sources such as reference lists, relevant review articles, and literature summary documents maintained by authors (Figure 1). After removing duplicates, 11 996 titles or abstracts remained and 967 were eligible for full-text screening. Full-text screening by two independent reviewers resulted in 97.5% agreement on inclusion or exclusion (kappa = 0.857). A total of 136 studies remained for inclusion in this systematic review and meta-analysis.

Study Characteristics

The study design, sample size, outcomes, and methods for PA assessment for the 136 included studies are shown in Table 1. Of these, nine studies reported on multiple cancer sites, 38 on all-cancer sites combined, 39 on breast cancer, 19 on colorectal cancer, nine on prostate cancer, four each for ovarian and pancreatic cancers, three each on endometrial and hematologic cancers, two for lung cancer, and one each for bladder cancer, cervical, childhood, kidney cancers, malignant glioma, and melanoma. To improve the precision of our estimates, we combined cervical, endometrial, and ovarian cancers as "female reproductive" cancers and leukemia, lymphoma, myeloma, and other hematopoietic cancers as "hematologic" cancers. The included studies were primarily of high quality (scores >7), with 38 studies receiving perfect scores on the Newcastle-Ottawa quality assessment (Table 1). The most common reasons for reductions on the quality assessment scale were the use of self-administered questionnaires to report PA behaviors (56% of studies used participant-reported or retrospective data collection to ascertain PA levels) and having nonrepresentative population samples (15% of included studies).

Primary Results

Figures 2 and 3 display forest plots of the summary hazard ratios for the highest vs lowest amount of prediagnosis and postdiagnosis PA for all cancers and specific cancer sites on cancer-specific mortality and all-cause mortality, respectively. Evidence from 136 studies contributed to findings showing reduced hazards of mortality for those in the highest vs lowest levels of prediagnosis and/or postdiagnosis total or recreational PA for all cancers combined (cancer-specific mortality: hazard ratio [HR] = 0.82, 95% confidence interval [CI] = 0.79 to 0.86, and HR = 0.63, 95% CI = 0.53 to 0.75, respectively). Statistically significantly reduced hazards were also found for 11 cancer types depending on timing of PA (prediagnosis and postdiagnosis) and mortality outcome (cancer-specific and all-cause mortality). Specifically, higher prediagnosis PA was protective against cancer-specific mortality following breast, colorectal, hematologic, liver, lung, and stomach cancer, and higher postdiagnosis PA was protective against cancer-specific mortality following breast, colorectal, and prostate cancer (Figure 2). For all-cause mortality, higher prediagnosis PA was protective against breast, colorectal, hematologic, and prostate cancer, and higher postdiagnosis PA was protective following breast, childhood,

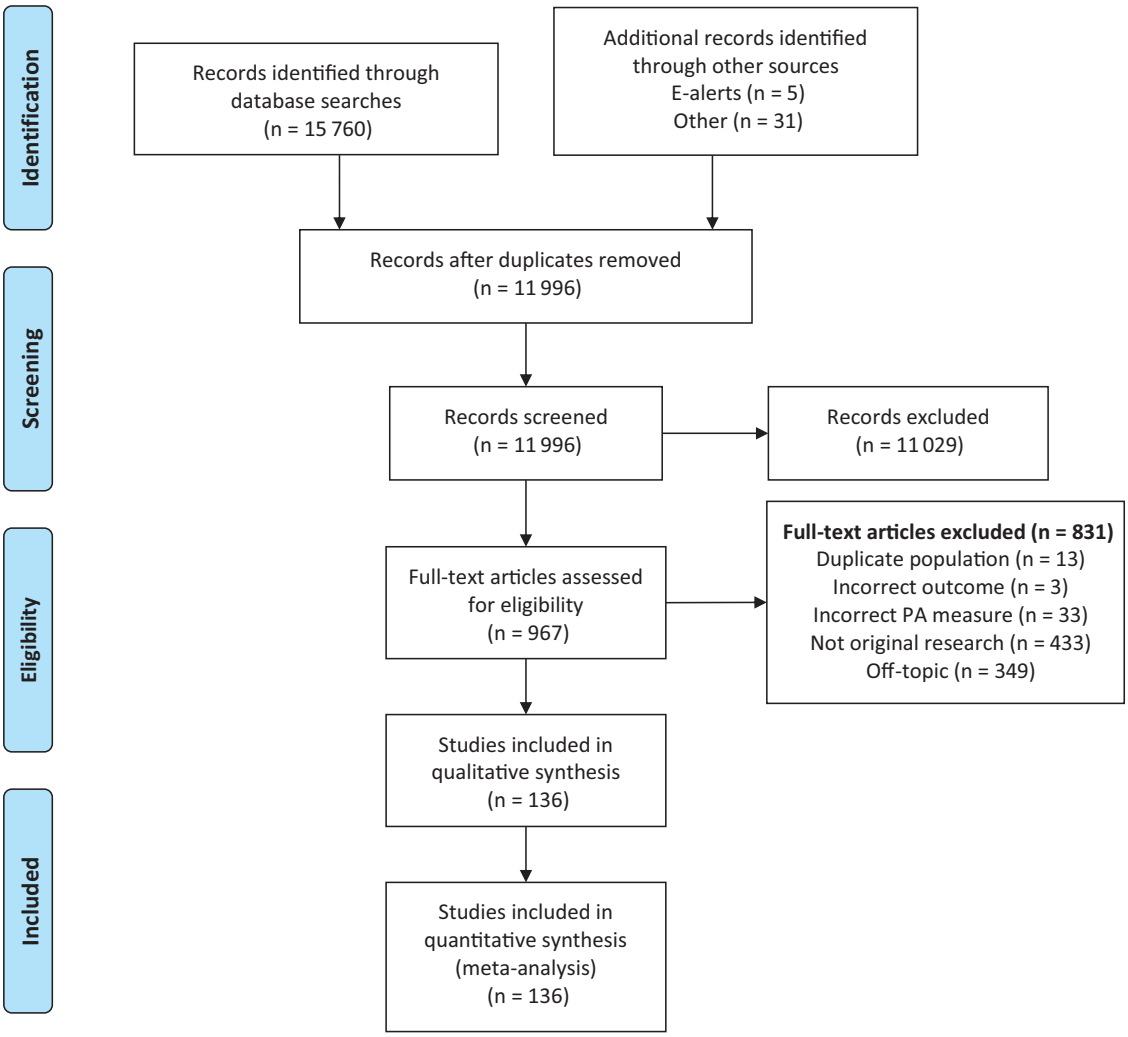

Figure 1. Flow diagram showing inclusion and exclusion of studies. PA = physical activity.

colorectal, gynecologic, glioma, hematologic, kidney, lung, prostate, and stomach cancer (Figure 3). Breast and colorectal cancer sites had the largest number of contributing studies, and results suggest that greater reductions were observed for postdiagnosis PA both for cancer-specific and all-cause mortality (HR = 0.58–0.63) compared with mortality reductions observed with prediagnosis PA (HR = 0.80–0.86). Summary estimates did not differ by time scale (Supplementary Table 1, available online), and thus healthy cohorts and cancer survival cohorts were combined in the results. Further, removal of randomized, controlled trials did not change the results (data not shown).

When considering the association between PA and CVD mortality and given the small number of studies, prediagnosis and postdiagnosis PA were combined to create a single estimate. The summary hazard ratios for all-cancer (n = 3), childhood cancer (n = 1), and colorectal cancer (n = 4) were 0.60 (95% CI = 0.50–0.73), 0.89 (95% CI = 0.49–1.61), and 0.60 (95% CI = 0.40–0.91), respectively. No cancer sites were found to have statistically significant increased mortality hazards (for any mortality outcome) associated with higher levels of PA (Supplementary Table 2, available online).

After visual examination of funnel plots and *P* values from the Begg and Egger tests, there was evidence for publication bias only for postdiagnosis PA and colorectal cancer-specific mortality ($P < .05$) (results not shown).

Subgroup Analysis Results

Subgroup analyses by sex, BMI, menopausal status (in breast cancer), and colorectal subtype are presented in Table 2. Overall, hazards of cancer-specific and all-cause mortality for those undertaking higher vs lower prediagnosis and/or postdiagnosis PA were reduced both for men and women (all cancers and within colorectal cancer), those with lower BMI (<25 kg/m^2; for all cancers, and within breast and colorectal but not within prostate cancer), prediagnosis and postmenopausal women (except for the association for premenopausal women and breast cancer-specific mortality), and colorectal subtypes, with trends toward stronger effect for postdiagnosis PA (HR = 0.37–0.88) vs prediagnosis PA (HR = 0.75–1.53).There was some suggestion (based on differences in effect size observed across colorectal, breast, and hematological cancer groups) that benefit through postdiagnosis PA to all-cause mortality survival was greater for those with BMI less than 25 kg/m^2 (HR = 0.49–0.57;

Table 1. Characteristics of the included studies in the systematic review and meta-analysis on physical activity and cancer mortality, by cancer site*

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Studies assessing multiple sites									
Davey Smith, 2000, United Kingdom (25)	Whitehall Study	All, lung, hematopoietic, stomach, pancreas	832	—	6702	Cancer-specific	Prediagnosis	—	7
Batty, 2001, United Kingdom (26)	Whitehall Study	All, lung, colorectal, hematopoietic, stomach, pancreas, colorectal	1499	—	11 663	Cancer-specific	Prediagnosis	CRC subsite	7
Sundelof, 2008, Sweden (27)	Swedish Oesophageal and Cardia Cancer Study	Esophagus, squamous cell, stomach	—	580	580	All-cause	Prediagnosis	—	9
Wen, 2011, Taiwan (28)	—	All, colorectal, liver, lung, breast	2185	—	416 175	Cancer-specific	Prediagnosis	Age, sex	8
Arem, 2014, United States (29)	National Institutes of Health–AARP Diet and Health Study	All, lymphocytic leukemia, liver, oral cavity and pharynx, non-Hodgkin lymphoma, esophagus, myeloma, lung, myeloid/monocytic leukemia, stomach, ovarian, prostate, bladder, breast, brain, endometrial, pancreas, kidney	15 001	—	293 511	Cancer-specific	Prediagnosis	—	8
Okada, 2017, Japan (30)	BioBank Japan Project	Esophagus, stomach	816	1939	1939	All-cause	Postdiagnosis	—	9
Jee, 2018, Korea (31)	Korean Metabolic Syndrome Mortality Study	All, esophagus, head and neck, liver, lung, colorectal, pancreas, kidney, stomach, prostate, breast, cervix	7539	—	303 428	Cancer-specific	Prediagnosis	No overall, by sex	8
Schmid, 2018, United States (32)	National Institutes of Health–AARP Diet and Health Study	Hematologic, non-Hodgkin lymphoma, myeloma, leukemia	2606	5182	5182	All-cause, cancer-specific	Prediagnosis, postdiagnosis	Age, sex, BMI	8
Tarasenko, 2018, United States (33)	National Health Interview Survey	All, breast, prostate, colorectal, uterine	3528	13 997	13 997	All-cause, cancer-specific, CVD-specific	Postdiagnosis	—	9
Studies assessing only all-cancer									
Arraiz, 1992, Canada (34)	Canada Health Survey Mortality Follow-up Study	All	229	—	12 917	Cancer-specific	Prediagnosis	—	9
Kampert, 1996, United States (35)	Aerobics Center Longitudinal Study	All	223	—	32 421	Cancer-specific	Prediagnosis	No overall, by sex	7

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Rosengren, 1997, Sweden (36)	Multifactor Primary Prevention Study	All	723	—	7142	Cancer-specific	Prediagnosis	Men only	8
Kilander, 2001, Sweden (37)	—	All	216	—	2285	Cancer-specific	Prediagnosis	Men only	8
Hu, 2005, Finland (38)	—	All	2039	—	47 212	Cancer-specific	Prediagnosis	No overall, by sex	8
Schnohr, 2006, Denmark (39)	Copenhagen City Heart Study	All	632	—	4894	Cancer-specific	Prediagnosis	—	8
Matthews, 2007, China (40)	Shanghai Women's Health Study	All	537	—	67 143	Cancer-specific	Prediagnosis	Women only	9
Orsini, 2008, Sweden (41)	Cohort of Swedish Men	All	901	—	37 633	Cancer-specific	Prediagnosis	No overall, by BMI, men only	8
van Dam, 2008, United States (42)	Nurses' Health Study	All	4527	—	77 782	Cancer-specific	Prediagnosis	Women only	7
Hamer, 2009, Scotland (43)	Scottish Health Surveys	All	78	293	293	All-cause	Postdiagnosis	Type of PA	9
Autenrieth, 2011, Germany (44)	MONICA/KORA Augsburg Survey (S2)	All	326	—	4672	Cancer-specific	Prediagnosis	Type of PA	9
Borch, 2011, Norway (45)	Norwegian Women and Cancer Cohort Study	All	1584	—	66 136	Cancer-specific	Prediagnosis	Women only	8
Laukkanen, 2011, Finland (46)	Eastern Finnish Follow-up Study	All	181	—	2560	Cancer-specific	Prediagnosis	Men only	9
McCullough, 2011, United States (47)	Cancer Prevention Study-II Nutrition Cohort	All	5874	—	111 966	Cancer-specific	Prediagnosis	No overall, by sex	8
Lin, 2012, Taiwan (48)	Taichung Diabetes Study	All	122	—	5686	Cancer-specific	Prediagnosis	—	8
Mok, 2012, Korea (49)	Severance Cohort Study	All	1060	3555	59 636	Cancer-specific	Prediagnosis	No overall, by sex	8
Parekh, 2012, United States (50)	Third National Health and Nutrition Examination Survey	All	860	—	15 535	Cancer-specific	Prediagnosis	BMI	9
Inoue-Choi, 2013, United States (51)	Iowa Women's Health Study	All	461	2017	2017	All-cause, cancer-specific, CVD-specific	Postdiagnosis	Women only	8
Vergnaud, 2013, Europe (52)	European Prospective Investigation into Cancer and Nutrition	All	9388	—	378 864	Cancer-specific	Prediagnosis	Sex	8

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Wang, 2013, China (53)	Shanghai Men's Health Study	All	1053	—	61 477	Cancer-specific	Prediagnosis	Men only	9
Yu, 2013, China (54)	—	All	452	—	2867	Cancer-specific	Prediagnosis	No overall, by sex	8
Gunnell, 2014, Australia (55)	Busselton Health Study	All	164	528	2320	Cancer-specific	Prediagnosis	—	8
Hardee, 2014, United States (56)	Aerobics Center Longitudinal Study	All	121	2863	2863	All-cause	Postdiagnosis	—	8
Hastert, 2014, United States (57)	Vitamins and Lifestyle Study	All	1595	—	57 841	Cancer-specific	Prediagnosis	—	8
Lee, 2014, United States (58)	Harvard Alumni Health Study	All	777	1021	1021	All-cause, cancer-specific, CVD-specific	Postdiagnosis	Men only	7
Wanner, 2014, Switzerland (59)	MONICA/National Research Program 1A	All	1351	—	17 663	Cancer-specific	Prediagnosis	Sex	8
Brown, 2015, United States (60)	Third National Health and Nutrition Examination Survey	All	319	416	416	All-cause	Prediagnosis	—	8
Kabat, 2015, United States (61)	National Institutes of Health–AARP Diet and Health Study	All	16 193	73 784	476 396	Cancer-specific	Prediagnosis	No overall, by sex	8
Kraschnewski, 2016, United States (62)	National Health Interview Survey	All	—	—	30 162	Cancer-specific	Prediagnosis	—	7
Lee, 2016, Korea (63)	Kangbuk Samsung Health Study	All	970	—	336 560	Cancer-specific	Prediagnosis	Age, sex, BMI	8
Robsahm, 2016, Norway (64)	Oslo Ischemia Study	All	433	758	1997	Cancer-specific	Prediagnosis	Men only, type of PA	8
Gunnell, 2017, Australia (65)	Western Australia Health and Wellbeing Surveillance System	All	135	1589	4734	All-cause, cancer-specific	Postdiagnosis	—	9
Kamada, 2017, United States (66)	Women's Health Study	All	748	—	28 879	Cancer-specific	Prediagnosis	Women only	8
O'Donovan, 2017, United Kingdom (67)	Health Survey for England and Scottish Health Survey	All	2526	—	63 591	Cancer-specific	Prediagnosis	—	9

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Vainshelboim, 2017, United States (68)	Veterans Exercise Testing Study	All	447	1013	4034	Cancer-specific	Prediagnosis	Men only	7
Dohrn, 2018, Sweden (69)	Sweden Attitude Behaviour and Change Study	All	27	—	851	Cancer-specific	Prediagnosis	—	9
Liu, 2018, China (70)	Shanghai Men's Health Study and Shanghai Women's Health Study	All	3512	—	120 727	Cancer-specific	Prediagnosis	Sex	9
Patel, 2018, United States (71)	Cancer Prevention Study–II Nutrition Cohort	All	13 186	—	139 255	Cancer-specific	Prediagnosis	—	8
Studies assessing only bladder cancer									
Liss, 2017, United States (72)	National Health Information Survey	Bladder	83	—	222 163	Cancer-specific	Prediagnosis	—	9
Studies assessing only breast cancer									
Rohan, 1995, Australia (73)	—	Breast	112	412	412	Cancer-specific	Prediagnosis	Menopausal status	9
Borugian, 2004, Canada (74)	—	Breast	112	603	603	Cancer-specific	Prediagnosis	Menopausal status	8
Enger, 2004, United States (75)	—	Breast	251	717	717	Cancer-specific	Prediagnosis	—	9
Holmes, 2005, United States (76)	Nurses' Health Study	Breast	463	2987	2987	All-cause, cancer-specific	Postdiagnosis	BMI, menopausal status	7
Abrahamson, 2006, United States (77)	—	Breast	290	1264	1264	All-cause	Prediagnosis	BMI	8
Dal Maso, 2008, Italy (78)	—	Breast	503	1453	1453	All-cause, cancer-specific	Prediagnosis	Type of PA	9
Holick, 2008, United States (79)	Collaborative Women's Longevity Study	Breast	412	4482	4482	All-cause, cancer-specific	Postdiagnosis	BMI, age	8
Irwin, 2008, United States (80)	Health, Eating, Activity, and Lifestyle Study	Breast	164	933	933	All-cause, cancer-specific	Prediagnosis, postdiagnosis	BMI, menopausal status	9
Friedenreich, 2009, Canada (81)	—	Breast	341	1225	1225	All-cause, cancer-specific	Prediagnosis	Type of PA	9
Sternfeld, 2009, United States (82)	Life After Cancer Epidemiology Study	Breast	187	1970	1970	All-cause, cancer-specific	Postdiagnosis	BMI	8
West-Wright, 2009, United States (83)	California Teachers Study	Breast	460	3539	3539	All-cause, cancer-specific	Prediagnosis	BMI	7

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Emaus, 2010, Norway (84)	Norwegian Counties Study	Breast	429	1364	1364	All-cause, cancer-specific	Prediagnosis	BMI, menopausal status	8
Hellmann, 2010, Denmark (85)	Copenhagen City Heart Study	Breast	323	528	528	All-cause, cancer-specific	Prediagnosis	Menopausal status	8
Keegan, 2010, United States, Canada, Australia (86)	Breast Cancer Family Registry	Breast	725	4153	4153	All-cause	Prediagnosis	BMI	8
Bertram, 2011, United States (87)	Women's Healthy Eating and Living Study	Breast	163	2361	2361	All-cause	Postdiagnosis	—	8
Chen, 2011, China (88)	Shanghai Breast Cancer Survival Study	Breast	436	4826	4826	All-cause	Postdiagnosis	BMI, menopausal status	9
Irwin, 2011, United States (89)	Women's Health Initiative	Breast	350	4643	4643	All-cause, cancer-specific	Prediagnosis, postdiagnosis	BMI	8
Beasley, 2012, United States, China (9)	After Breast Cancer Pooling Project: LACE-NHS-SBCSS-WHEL	Breast	1468	13 302	13 302	All-cause, cancer-specific	Postdiagnosis	BMI, menopausal status	7
Cleveland, 2012, United States (90)	Long Island Breast Cancer Study Project	Breast	196	1508	1508	All-cause, cancer-specific	Prediagnosis	BMI, menopausal status	9
Schmidt, 2013, Germany (91)	MARIE Study	Breast	367	3393	3393	All-cause, cancer-specific	Prediagnosis	BMI	9
Tao, 2013, United States (92)	Western New York Exposure and Breast Cancer Study	Breast	170	1170	1170	All-cause, cancer-specific	Prediagnosis	—	9
Williams, 2013, United States (93)	National Runners' and Walkers' Health Survey	Breast	111	—	79 124	Cancer-specific	Prediagnosis	—	7
Bradshaw, 2014, United States (94)	Long Island Breast Cancer Study	Breast	420	1423	1423	All-cause, cancer-specific	Postdiagnosis	BMI	9
Courneya, 2014, Canada (95)	Supervised Trial of Aerobic vs Resistance Training	Breast	24	242	242	All-cause	Postdiagnosis	—	9
de Glas, 2014, Netherlands (96)	Tamoxifen Exemestane Adjuvant Multicenter Lifestyle Study	Breast	80	521	521	All-cause, cancer-specific	Prediagnosis	Age	6

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Keegan, 2014, United States (97)	Neighborhoods and Breast Cancer Study	Breast	915	4345	4345	All-cause, cancer-specific	Prediagnosis	—	9
Williams, 2014, United States (98)	National Runners' and Walkers' Health Survey	Breast	46	986	986	Cancer-specific	Postdiagnosis	—	7
Bao, 2015, China (99)	Shanghai Breast Cancer Survival Study	Breast	128	518	518	All-cause	Postdiagnosis	Triple negative only	9
Borch, 2015, Norway (100)	Norwegian Women and Cancer Cohort Study	Breast	197	1327	1327	All-cause, cancer-specific	Prediagnosis, postdiagnosis	BMI, menopausal status	8
Lu, 2015, United States (101)	California Breast Cancer Survivorship Consortium	Breast	1347	4608	4608	All-cause, cancer-specific	Prediagnosis	BMI, menopausal status	9
Pinkston, 2015, United States (102)	New Mexico Women's Health Study	Breast	240	540	1283	All-cause, cancer-specific	Prediagnosis	No overall, by race and type of PA	9
Ammitzboll 2016, Denmark (103)	Diet, Cancer and Health Study	Breast	144	959	959	All-cause	Postdiagnosis	Type of PA	7
Jones, 2016, United States (104)	Life After Cancer Epidemiology and Pathways studies	Breast	405	6211	6211	Cancer-specific	Postdiagnosis	—	8
McCullough, 2017, United States (105)	Long Island Breast Cancer Study	Breast	486	1254	1254	All-cause, cancer-specific	Prediagnosis	—	7
Cifu, 2018, United States (106)	National Institutes of Health–AARP Diet and Health Study	Breast	1162	7088	7088	Cancer-specific	Prediagnosis	—	8
Hayes, 2018, Australia (107)	Exercise for Health Trials	Breast	26	337	337	All-cause	Postdiagnosis	BMI, menopausal status	7
Maliniak, 2018, United States (108)	Cancer Prevention Study-II Nutrition Cohort	Breast	1771	5254	5254	All-cause, cancer-specific	Prediagnosis, postdiagnosis	No overall, by age	8
Palesh, 2018, United States (109)	—	Breast	93	103	103	All-cause	Postdiagnosis	—	8
Parada, 2019, United States (110)	Carolina Breast Cancer Study	Breast	717	1808	1808	All-cause	Prediagnosis	—	9
Studies assessing only cervical cancer									
Kim, 2016, Korea (111)	—	Cervical	30	860	860	All-cause	Postdiagnosis	—	8
Studies assessing only childhood cancer									
Scott, 2018, United States Canada (112)	Childhood Cancer Survivor Study	Childhood cancer	1063	15 450	15 450	All-cause, CVD-specific	Postdiagnosis	—	8

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Studies assessing only colorectal cancer									
Meyerhardt, 2006, United States (113)	Nurses' Health Study	Colorectal	132	573	573	All-cause, cancer-specific	Prediagnosis; postdiagnosis	Women only, age, BMI, colon vs rectum	7
Huxley, 2007, China, Hong Kong, Japan, Korea, Singapore, Taiwan, Thailand, Australia, New Zealand (114)	Asia Pacific Cohort Studies Collaboration	Colorectal	751	—	539 201	Cancer-specific	Prediagnosis	—	6
Meyerhardt, 2009, United States (115)	Health Professionals Follow-Up Study	Colorectal	258	668	668	All-cause, cancer-specific	Postdiagnosis	Men only	7
Baade, 2011, Australia (116)	—	Colorectal	462	1825	1825	All-cause, CVD-specific	Postdiagnosis	Age, sex, BMI, colon vs rectum	8
Morrison, 2011, United Kingdom (117)	Whitehall Study	Colorectal	450	—	17 949	Cancer-specific	Prediagnosis	No overall, by colon vs rectum	7
Kuiper, 2012, United States (118)	Women's Health Initiative	Colorectal	265	1339	1339	All-cause, cancer-specific	Prediagnosis, postdiagnosis	Women only	8
Boyle, 2013, Australia (119)	Western Australia Bowel Health Study	Colorectal	224	879	879	All-cause, cancer-specific	Prediagnosis	Sex, colon vs rectum	8
Campbell, 2013, United States (120)	Cancer Prevention Study-II Nutrition Cohort	Colorectal	846	2293	2293	All-cause, cancer-specific, CVD-specific	Prediagnosis, postdiagnosis	Age, sex, BMI, colon vs rectum	8
Pelser, 2014, United States (121)	National Institutes of Health–AARP Diet and Health Study	Colorectal	1727	5727	5727	All-cause, cancer-specific, CVD-specific	Prediagnosis,	No overall, by colon vs rectum	8
Arem, 2015, United States (122)	National Institutes of Health–AARP Diet and Health Study	Colorectal	1541	3797	3797	All-cause, cancer-specific, CVD-specific	Prediagnosis, postdiagnosis	—	8
Hardikar, 2015, United States (123)	Colon Cancer Family Registry-Seattle	Colorectal	408	1309	1309	All-cause, cancer-specific	Prediagnosis	Colon vs rectum	8
Romaguera, 2015, Europe (124)	European Prospective Investigation into Cancer and Nutrition	Colorectal	1113	3292	3292	All-cause, cancer-specific	Prediagnosis	—	8
Mok, 2016, Korea (125)	Korean Metabolic Syndrome Mortality Study	Colorectal	469	—	226 089	Cancer-specific	Prediagnosis	No overall, by sex, colon vs rectum, age, BMI	8

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Thong, 2016, Netherlands (126)	Patient-Reported Outcomes Following Initial Treatment and Long-Term Evaluation of Survivorship registry	Colorectal	249	1552	1552	All-cause	Postdiagnosis	—	6
Ratjen, 2017, Germany (127)	—	Colorectal	200	1376	1376	All-cause	Postdiagnosis	Type of PA, sex, age, BMI, colon vs rectum	8
Walter, 2017, Germany (128)	DACHS Study	Colorectal	868	3121	3121	All-cause, cancer-specific	Prediagnosis	Age, sex, colon vs rectum, BMI	9
Jayasekara, 2018, Australia (129)	Melbourne Collaborative Cohort Study	Colorectal	339	724	724	All-cause, cancer-specific	Prediagnosis	Colon vs rectum	9
Phipps, 2018, United States (130)	North Central Cancer Treatment Group N0147	Colorectal	505	1992	1992	All-cause	Prediagnosis	Colon only	7
van Blarigan, 2018, United States (131)	Cancer and Leukemia Group B 89803	Colorectal	299	992	992	All-cause	Postdiagnosis	Colon only	8
Studies assessing only endometrial cancer									
Arem, 2013, United States (132)	National Institutes of Health–AARP Diet and Health Study	Endometrial	312	1400	1400	All-cause	Prediagnosis	—	8
Arem, 2013, United States (133)	Women's Health Initiative	Endometrial	163	983	983	All-cause, cancer-specific	Prediagnosis	—	8
Arem, 2016, United States (134)	National Institutes of Health–AARP Diet and Health Study	Endometrial	91	580	580	All-cause	Postdiagnosis	—	8
Studies assessing only malignant glioma									
Ruden, 2011, United States (135)	—	Malignant glioma	149	243	243	All-cause	Postdiagnosis	—	7
Studies assessing only hematologic cancers									
Wiskemann, 2015, Germany (136)	—	Leukemia	44	103	103	All-cause	Postdiagnosis	—	6
Boyle, 2017, Canada (137)	—	Lymphoma	169	413	413	All-cause, cancer-specific	Prediagnosis	—	6
Pophali, 2018, United States (138)	Lymphoma SPORE Molecular Epidemiology Resource	Lymphoma	863	3060	3060	All-cause, cancer-specific	Prediagnosis	—	8

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Studies assessing only kidney cancer									
Schmid, 2018, United States (139)	National Institutes of Health–AARP Diet and Health Study	Kidney	175	667	667	All-cause, cancer-specific	Postdiagnosis	—	8
Studies assessing only lung cancer									
Jones, 2012, United States (140)	—	Lung	77	118	118	All-cause	Postdiagnosis	—	7
Sloan, 2016, United States (141)	Mayo Clinic Epidemiology and Genetics of Lung Cancer Research Program	Lung	512	1466	1466	All-cause	Postdiagnosis	—	7
Studies assessing only melanoma									
Schwitzer, 2017, Australia, Canada, Italy, United States (142)	Genes, Environment and Melanoma Study	Melanoma	341	2465	2465	All-cause, cancer-specific	Prediagnosis	—	9
Studies assessing only ovarian cancer									
Yang, 2008, Sweden (143)	—	Ovarian	396	635	635	Cancer-specific	Prediagnosis	—	8
Moorman, 2011, United States (144)	North Carolina Ovarian Cancer Study	Ovarian	238	638	1321	All-cause	Prediagnosis	—	9
Zhou, 2014, United States (145)	Women's Health Initiative	Ovarian	346	600	600	All-cause, cancer-specific	Prediagnosis	—	8
Abbott, 2018, United States (146)	African American Cancer Epidemiology Study	Ovarian	80	264	264	All-cause	Prediagnosis, postdiagnosis	—	9
Studies assessing only pancreatic cancer									
Lee, 2003, United States (147)	College Alumni Health Study	Pancreatic	212	—	32 687	Cancer-specific	Prediagnosis	—	7
Lin, 2007, Japan (148)	Japanese Collaborative Cohort Study	Pancreatic	402	—	100 932	Cancer-specific	Prediagnosis	No overall, by sex	8
Stevens, 2009, United Kingdom (149)	Million Women Study	Pancreatic	1710	—	1 290 000	Cancer-specific	Prediagnosis	Women only	8
Nakamura, 2011, Japan (150)	Takayama Study	Pancreatic	52	—	30 826	Cancer-specific	Prediagnosis	No overall, by sex	8

(continued)

Table 1. (continued)

Author, year, country, reference	Name of study	Cancer type	No. deaths	No. with cancer	No. in analytic sample	Outcome type	Physical activity assessment	Subgroups used	Quality score (of 9)
Studies assessing only prostate cancer									
Nilsen, 2006, Norway (151)	HUNT Study (Norway)	Prostate	354	957	29 110	Cancer-specific	Prediagnosis	—	8
Crespo, 2008 (152) Puerto Rico	Puerto Rico Heart Health Program	Prostate	167	—	9780	Cancer-specific	Prediagnosis	BMI, age	9
Orsini, 2009, Sweden (153)	Cohort of Swedish Men	Prostate	190	—	45 887	Cancer-specific	Prediagnosis	Type of PA	8
Batty, 2011, United Kingdom (154)	Whitehall Study	Prostate	578	—	17 934	Cancer-specific	Prediagnosis	Type of PA	7
Kenfield, 2011, United States (155)	Health Professionals Follow-Up Study	Prostate	548	2705	2705	All-cause, cancer-specific	Postdiagnosis	—	7
Bonn, 2015, Sweden (156)	Progression in Cancer of the Prostate	Prostate	561	4623	4623	All-cause, cancer-specific	Postdiagnosis	Type of PA	8
Friedenreich, 2016, Canada (157)	—	Prostate	458	830	830	All-cause, cancer-specific	Prediagnosis, postdiagnosis	Type of PA	9
Tai, 2016, Taiwan (158)	—	Prostate	48	608	608	Cancer-specific	Prediagnosis	—	7
Wang, 2017, United States (159)	Cancer Prevention Study-II Nutrition Cohort	Prostate	454	7328	7328	All-cause, cancer-specific	Prediagnosis, postdiagnosis	—	8

*BMI = body mass index; CRC = colorectal cancer; CVD = cardiovascular disease; PA = physical activity.

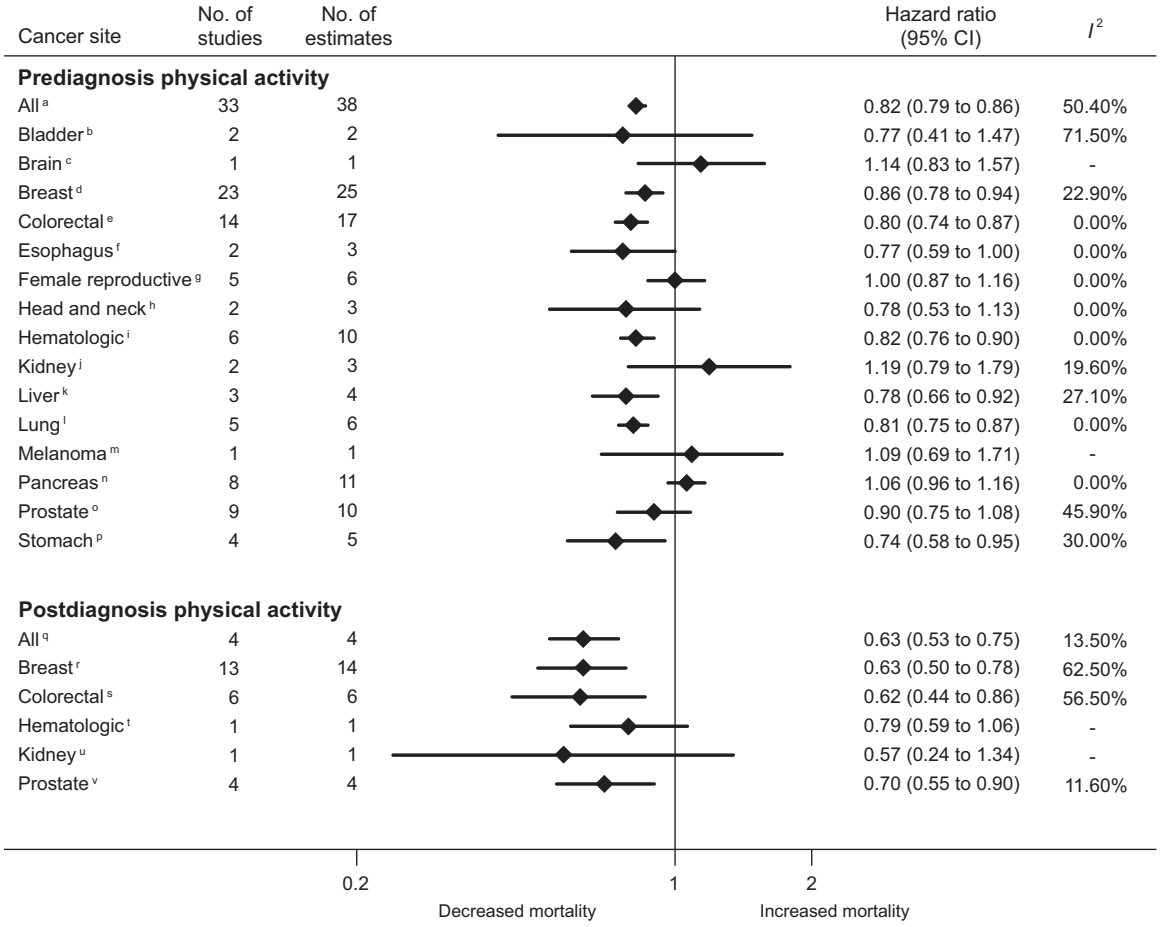

Figure 2. Summary hazard ratios for the highest vs lowest levels of prediagnosis and postdiagnosis physical activity and cancer-specific mortality by cancer site (each estimate denotes a separate meta-analysis performed; if only one estimate is present, then no meta-analyses were conducted and the individual point estimate is reported). [a]Refs. (25,26,28,29,31,34–39,41,42,44–46,48–50,52,54,55,57,59,62–64,66–71). [b]Refs. (29,72). [c]Refs. (29). [d]Refs. (28,31,73–75,78,80,81,83–85,89,91–93,96,97,100–102,105,106,108). [e]Refs. (26,28,31,113,114,117–120,122–124,128,129). [f]Refs. (29,31). [g]Refs. (29,31,132,143,145). [h]Refs. (29,31). [i]Refs. (25,26,29,137–139). [j]Refs. (29,31). [k]Refs. (28,29,31). [l]Refs. (25,26,28,29,31). [m]Refs. (142). [n]Refs. (25,26,29,31,147–150). [o]Refs. (29,31,151–154,157–159). [p]Refs. (25,26,29,31). [q]Refs. (33,51,55,58). [r]Refs. (9,76,79,80,82,88,89,93,94,96,100,104,108). [s]Refs. (113,115,116,118,120,122). [t]Refs. (32). [u]Refs. (139). [v]Refs. (155–157,159). CI = confidence interval.

all $P < .05$) compared with those with BMI greater than 25 kg/m^2 (HR = 0.64–0.71; $P < .05$–0.112).

PA Domain Results

Additional subgroup analyses by domain of PA (total, recreational, transportation, occupational, and household) are presented in Table 3. For prediagnosis PA, the domains of recreational and total PA estimates were consistently associated with reduced hazards of mortality for all-cancer, breast, and colorectal cancer-specific mortality ($P < .05$). Results remained inconsistent for the less-studied domains of transportation, occupational, and household PA (HR = 0.64–1.65).

Dose-Response Analyses

We restricted the analysis of dose-response to breast cancer studies because few studies examined these associations for other cancer sites. There was a linear association between prediagnosis PA dose and all-cause mortality (P for nonlinearity = .53) (Figure 4C). Evidence of nonlinear associations was found (P for nonlinearity <.05) between prediagnosis and postdiagnosis PA and breast cancer-specific mortality (Figure 4, A and B, respectively) and postdiagnosis PA and all-cause mortality (Figure 4D). As seen in Figure 4B, the dose-response curve for postdiagnosis PA and all-cause mortality shows the largest reductions in mortality. Compared with no recreational PA, 5, 10, 20, 30, and 65 MET hours per week reduced all-cause mortality by 22%, 43%, 59%, 69%, and 108%, respectively. The steep reductions in mortality seen in Figure 4, A, B, and D, become less pronounced when PA dose is 10–15 MET hours per week or greater. The upper bounds of Figure 4C are less precise because of few contributing studies at higher levels of PA.

Discussion

In this first ever analysis, to our knowledge, of the association between PA and cancer survival that included all cancer sites, we found evidence from 136 studies conducted to date for improved survival outcomes for all cancer and 11 cancer sites associated with prediagnosis or postcancer diagnosis PA. Although the most consistent and strong evidence for a role of PA in cancer survival was found for breast and colorectal cancer, there is also clear evidence for improved prostate cancer-specific survival with

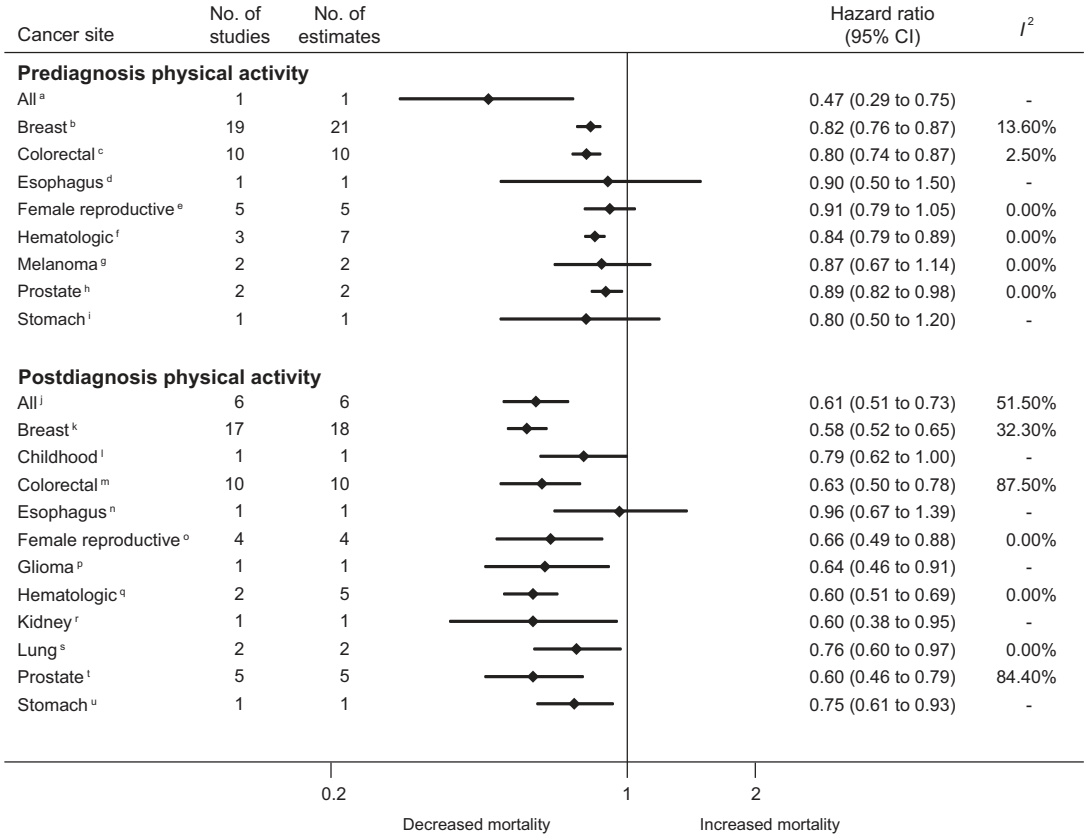

Figure 3. Summary hazard ratios for the highest vs lowest levels of prediagnosis and postdiagnosis physical activity and all-cause mortality in cancer survivors by cancer site (each estimate denotes a separate meta-analysis performed; if only one estimate is present, then no meta-analyses were conducted and the individual point estimate is reported). [a]Refs. (60). [b]Refs. (77,78,80,81,83–86,89,91,92,96,97,100–102,105,108,110). [c]Refs. (113,118–120,122–124,128–130). [d]Refs. (27). [e]Refs. (132,144–146). [f]Refs. (32,137,138). [g]Refs. (27,142). [h]Refs. (157,159). [i]Refs. (27). [j]Refs. (33,43,51,55,56,58). [k]Refs. (9,33,76,79,80,82,87–89,94–96,100,103,107–109). [l]Refs. (112). [m]Refs. (33,113,115,116,118,120,122,126,127,131). [n]Refs. (30). [o]Refs. (33,111,134,146). [p]Refs. (135). [q]Refs. (136,139). [r]Refs. (139). [s]Refs. (140,141). [t]Refs. (33,155–157,159). [u]Refs. (30). CI = confidence interval.

postdiagnosis PA. In addition, there is emerging evidence for a beneficial effect of prediagnosis PA on cancer-specific survival for liver, lung, hematologic, esophageal, and stomach cancers. Compared with prediagnosis PA, postdiagnosis PA was associated with greater reductions both in cancer-specific and all-cause mortality, with greater than 30% reductions in hazards for all-cause mortality observed in studies of all cancer, breast, colorectal, female reproductive, glioma, kidney, lung, prostate, and stomach cancers (HR = 0.58–0.76).

This study extends the results found in previous meta-analyses of PA and cancer survival (5,6,8–12), with our results for breast and colorectal cancer similar in magnitude to those previously reported (4–6,10) (prediagnosis and postdiagnosis PA HR = ∼ 0.80 and 0.60, respectively, for cancer-specific and all-cause mortality). Findings reported here also indicate that PA contributes to survival benefits for prostate, lung, liver, hematologic, stomach, esophageal, and female reproductive cancers. Conversely, there was no evidence of harm from higher PA levels, even for cancers associated with poor prognosis (eg, lung cancer) or melanoma, which is the only cancer site for which higher levels of PA have been associated with higher risk of development.

Using data from studies involving women with breast cancer, we found a nonlinear relationship between increasing postdiagnosis PA levels and breast cancer-specific and all-cause mortality hazards, up to about 10–15 MET hours per week. This level is consistent with approximately 150 weekly minutes of moderate-intensity PA or 75 weekly minutes of vigorous-intensity PA and fits with the amount of PA recommended by the World Health Organization for healthy adults (160). This amount of PA is also typically endorsed and recommended by international cancer and clinical groups for those with cancer (13). Our findings also suggest that the clinical relevance of any potential survival benefit accrued through PA levels beyond 15 MET hours per week becomes less clear.

Questions remain regarding what represents the optimal dose, domain, and timing of activity for people with cancer and what these associations are for specific cancer sites or population subgroups. Findings from this meta-analysis show that there is clear evidence that postdiagnosis PA is an important independent prognostic factor distinct from prediagnosis activity levels. In addition, there is some preliminary evidence from three RCTs that exercise during treatment is also an important predictor of mortality outcomes (95,107,136). PA is also beneficial, irrespective of menopausal status, BMI, and sex, although being overweight or obese may attenuate the survival benefit. These findings highlight the need to combine weight (particularly fat mass) loss and PA interventions postcancer for those with BMIs greater than 25 kg/m^2. Currently, there are insufficient data to support specific recommendations related to

Table 2. Subgroup meta-analyses of the association between physical activity and cancer mortality, separately by sex, BMI, menopausal status, and colorectal subsite*

	Prediagnosis physical activity				Postdiagnosis physical activity			
Subgroup	No. of studies/ No. of estimates	HR (95% CI)	*P*	I^2	No. of studies/ No. of estimates	HR (95% CI)	*P*	I^2
Cancer-specific mortality								
Sex								
All cancers (male)	18/18	0.80 (0.74 to 0.87)	<.001	75.50%	1/1	0.62 (0.44 to 0.87)	.006	–
All cancers (female)	16/16	0.86 (0.79 to 0.93)	<.001	61.70%	1/1	0.72 (0.47 to 1.10)	.130	–
Colorectal (male)	3/3	0.85 (0.53 to 1.34)	.478	76.50%	2/2	0.70 (0.38 to 1.28)	.247	66.60%
Colorectal (female)	5/5	0.67 (0.54 to 0.84)	.001	0.00%	3/3	0.50 (0.27 to 0.90)	.020	58.10%
BMI								
All cancers (<25 kg/m^2)	3/3	0.77 (0.62 to 0.96)	.018	0.00%	–	–	–	–
All cancers (≥25 kg/m^2)	2/2	0.91 (0.66 to 1.25)	.568	0.00%	–	–	–	–
Breast (<25 kg/m^2)	4/4	0.92 (0.58 to 1.23)	.56	42.60%	7/7	0.59 (0.44 to 0.78)	<.001	49.70%
Breast (≥25 kg/m^2)	4/4	0.76 (0.48 to 1.22)	.258	73.40%	7/8	0.61 (0.50 to 0.75)	<.001	50.20%
Colorectal (<25 kg/m^2)	2/3	0.75 (0.59 to 0.96)	.021	19.20%	2/2	0.37 (0.07 to 1.94)	.239	71.80%
Colorectal (≥25 kg/m^2)	2/3	0.79 (0.61 to 1.02)	.070	0.00%	2/2	0.78 (0.34 to 1.66)	.485	66.80%
Prostate (<25 kg/m^2)	1/1	1.07 (0.55 to 2.11)	.844	–	–	–	–	–
Prostate (≥25 kg/m^2)	1/1	1.53 (0.81 to 2.91)	.192	–	–	–	–	–
Menopausal status								
Breast (premenopausal)	5/5	1.11 (0.90 to 1.37)	.310	0.00%	5/5	0.65 (0.47 to 0.89)	.008	45.50%
Breast (postmenopausal)	7/7	0.93 (0.79 to 1.09)	.347	0.00%	7/7	0.68 (0.55 to 0.84)	<.001	48.60%
Colorectal subsite								
Colon	8/9	0.94 (0.80 to 1.11)	.448	34.80%	2/2	0.76 (0.58 to 0.99)	.044	0.00%
Rectum	8/9	0.79 (0.67 to 0.94)	.007	0.00%	2/2	0.60 (0.19 to 1.88)	.378	71.00%
All-cause mortality in cancer survivors								
Sex								
All cancers (male)	–	–	–	–	1/1	0.52 (0.42 to 0.65)	<.001	–
All cancers (female)	–	–	–	–	1/1	0.62 (0.47 to 0.83)	.001	–
Colorectal (male)	3/3	0.73 (0.62 to 0.87)	<.001	0.00%	3/3	0.67 (0.56 to 0.80)	<.001	0.00%
Colorectal (female)	5/5	0.73 (0.59 to 0.91)	.006	18.00%	4/4	0.45 (0.30 to 0.68)	<.001	49.40%
BMI								
Breast (<25 kg/m^2)	7/7	0.74 (0.60 to 0.91)	.005	56.70%	7/7	0.49 (0.35 to 0.68)	<.001	64.20%
Breast (≥25 kg/m^2)	7/8	0.81 (0.71 to 0.93)	.002	0.00%	7/11	0.70 (0.60 to 0.82)	<.001	24.30%
Colorectal (<25 kg/m^2)	1/1	0.78 (0.58 to 1.05)	.101	–	2/2	0.57 (0.45 to 0.73)	<.001	0.00%
Colorectal (≥25 kg/m^2)	2/2	0.73 (0.58 to 0.92)	.009	0.00%	2/3	0.71 (0.47 to 1.08)	.112	38.60%
Hematologic (<25 kg/m^2)	1/1	0.80 (0.67 to 0.96)	.015	–	1/1	0.54 (0.36 to 0.79)	.002	–
Hematologic (≥25 kg/m^2)	1/1	0.83 (0.74 to 0.93)	.001	–	1/1	0.64 (0.50 to 0.82)	<.001	–
Menopausal status								
Breast (premenopausal)	4/4	0.86 (0.61 to 1.22)	.394	30.70%	4/4	0.77 (0.58 to 1.02)	.065	28.60%
Breast (postmenopausal)	6/6	0.81 (0.70 to 0.94)	.006	31.50%	5/5	0.69 (0.63 to 0.77)	<.001	0.00%
Colorectal subsite								
Colon	7/7	0.84 (0.71 to 0.99)	.037	56.60%	3/3	0.56 (0.42 to 0.75)	<.001	42.30%
Rectum	6/6	0.84 (0.70 to 1.00)	.056	23.00%	2/2	0.88 (0.67 to 1.14)	.321	0.00%

*BMI = body mass index; CI = confidence interval; HR = hazard ratio.

domain and dose of activity. For example, from a survival perspective, these epidemiologic findings support a PA dose of at least 10 METs, but not whether that dose is accumulated through recreational, transportation, occupational, or household activity, or mixed mode (aerobic vs resistance vs combined exercise) or specific intensity (moderate vs vigorous vs mixed). Nonetheless, findings are sufficiently compelling to support additional epidemiologic research, particularly on understudied cancer sites, subgroups within cancer sites, and more comprehensive measurement of PA (including during and posttreatment and domain, type, intensity, duration, and frequency). Further, these findings support the need for adequately powered, randomized, controlled exercise interventions that seek to evaluate the impact of modifying recreational PA on cancer outcomes (161–164).

The magnitude of the effect of PA on cancer-specific and all-cause mortality outcomes ranged from 0.46 to 1.19 for prediagnosis PA and cancer-specific survival, whereas for postdiagnosis activity the range was narrower and stronger (0.57–0.79 for cancer-specific survival). The range of effect sizes observed was similar for prediagnosis and postdiagnosis activity when considering all-cause mortality outcomes. For prediagnosis activity, estimates ranged from 0.47 to 0.92, and for postdiagnosis, the range was 0.37–0.96. Of interest, however, was that for cancer sites for which there were greater than 10 contributing point estimates (which occurred for all cancers combined, breast,

Table 3. Subgroup meta-analyses of the association between physical activity and cancer mortality, separately by domain of physical activity*

Site	PA type	No. of studies/ No. of estimates	HR (95% CI)	P	I^2	No. of studies/ No. of estimates	HR (95% CI)	P	I^2
Cancer-specific mortality									
All	Total	12/16	0.83 (0.75 to 0.92)	<.001	48.10%	2/2	0.66 (0.50 to 0.86)	.002	0.00%
	Recreational	24/27	0.82 (0.77 to 0.86)	<.001	68.20%	2/2	0.50 (0.24 to 1.02)	.057	67.80%
	Transportation	2/2	0.94 (0.82 to 1.07)	.362	0.00%	—	—	—	—
	Occupational	2/2	1.18 (0.70 to 1.98)	.530	61.00%	—	—	—	—
	Household	1/1	0.90 (0.54 to 1.49)	.684	—	—	—	—	—
Breast	Total	5/6	0.79 (0.63 to 0.99)	.043	0.00%	3/3	0.75 (0.47 to 1.21)	.236	0.00%
	Recreational	19/21	0.84 (0.75 to 0.94)	.002	35.40%	10/11	0.61 (0.47 to 0.78)	<.001	70.40%
	Transportation	—	—	—	—	—	—	—	—
	Occupational	2/2	1.03 (0.80 to 1.33)	.802	0.00%	—	—	—	—
	Household	1/1	1.25 (0.81 to 1.94)	.317	—	—	—	—	—
Colorectal	Total	2/2	0.84 (0.73 to 0.96)	.010	0.00%	1/1	0.88 (0.68 to 1.15)	.340	—
	Recreational	10/12	0.78 (0.70 to 0.87)	<.001	0.00%	5/7	0.48 (0.34 to 0.67)	<.001	10.50%
	Transportation	1/2	1.00 (0.63 to 1.58)	.989	0.00%	—	—	—	—
	Occupational	—	—	—	—	—	—	—	—
	Household	—	—	—	—		—	—	—
Prostate	Total	3/3	0.94 (0.70 to 1.27)	.697	7.20%	2/2	0.55 (0.36 to 0.87)	.010	0.00%
	Recreational	7/7	0.85 (0.70 to 1.04)	.108	44.70%	3/3	0.71 (0.56 to 0.91)	.007	14.30%
	Transportation	1/1	1.65 (0.87 to 3.14)	.127	—	1/1	0.64 (0.43 to 0.95)	.025	—
	Occupational	2/2	0.89 (0.59 to 1.35)	.580	0.00%	1/1	0.90 (0.53 to 1.54)	.700	—
	Household	1/1	0.78 (0.49 to 1.24)	.294	—	2/2	1.02 (0.76 to 1.36)	.911	0.00%
All-cause mortality in cancer survivors									
All	Total	—	—	—	—	3/3	0.55 (0.47 to 0.65)	<.001	0.00%
	Recreational	1/1	0.47 (0.29 to 0.75)	.002	—	5/5	0.63 (0.50 to 0.79)	<.001	50.80%
	Transportation	—	—	—	—	—	—	—	—
	Occupational	—	—	—	—	—	—	—	—
	Household	—	—	—	—	1/1	1.04 (0.60 to 1.80)	.889	—
Breast	Total	5/6	0.84 (0.67 to 1.05)	.126	32.80%	6/6	0.60 (0.47 to 0.75)	<.001	0.00%
	Recreational	16/18	0.81 (0.76 to 0.87)	<.001	16.70%	11/12	0.58 (0.51 to 0.66)	<.001	47.10%
	Transportation	—	—	—	—	—	—	—	—
	Occupational	2/2	1.09 (0.88 to 1.35)	.421	0.00%	—	—	—	—
	Household	1/1	1.46 (1.02 to 2.09)	.039	—	1/1	0.93 (0.55 to 1.55)	.784	—
Colorectal	Total	2/2	0.92 (0.80 to 1.06)	.237	0.00%	3/3	0.77 (0.57 to 1.03)	.080	84.60%
	Recreational	8/8	0.76 (0.70 to 0.84)	<.001	0.00%	7/9	0.58 (0.49 to 0.69)	<.001	11.60%
	Transportation	—	—	—	—	—	—	—	—
	Occupational	—	—	—	—	—	—	—	—
	Household	—	—	—	—	1/1	0.83 (0.55 to 1.23)	.364	—
Prostate	Total	1/1	1.02 (0.77 to 1.35)	.89		2/2	0.47 (0.31 to 0.71)	<.001	68.90%
	Recreational	2/2	0.87 (0.80 to 0.96)	.004	0.00%	4/4	0.69 (0.56 to 0.85)	<.001	71.80%
	Transportation	—	—	—	—	1/1	0.64 (0.43 to 0.94)	.025	—
	Occupational	1/1	1.35 (1.00 to 1.81)	.047	—	1/1	0.64 (0.47 to 0.91)	.011	—
	Household	1/1	0.91 (0.70 to 1.18)	.474	—	2/2	0.82 (0.70 to 0.97)	.023	0.00%

*CI = confidence interval; HR = hazard ratio; PA = physical activity.

colorectal, and prostate cancers), there was greater consistency of the evidence. This range of effect sizes for cancer-specific survival was reduced to 0.80–0.90 for prediagnosis PA and 0.62–0.70 for postdiagnosis PA, and for all-cause survival, the range was 0.80–0.82 for prediagnosis PA and 0.58–0.63 for postdiagnosis PA. Hence, as the evidence base is accumulating, despite differences in study populations, study designs, and PA assessment methods, there is remarkable consistency of the effects of prediagnosis and postdiagnosis PA across various cancer sites.

Despite the exponential increase in the number of studies conducted on this topic since the mid-2000s, there is still a paucity of evidence for most cancer sites with only breast, colorectal, and prostate cancers approaching the number of studies required per site for meta-analyses by site and within population subgroups. To understand whether current differences observed in effect size are cancer specific or due to imprecision, more research beyond these top three cancer sites is needed. Additional limitations of this meta-analysis include the heterogeneous PA assessment methods. We mitigated, as much as possible, the impact of different PA assessment methods by selecting, wherever possible, point estimates expressed in units of MET hours per week. In addition, differences in adjustment for confounding and examination of effect modification also make comparisons across studies more challenging and can adversely influence the precision of summary estimates reported. We examined this issue with our quality assessment of the 136 included studies, which determined that these studies, overall, had high quality of conduct, adding credibility to the findings reported here.

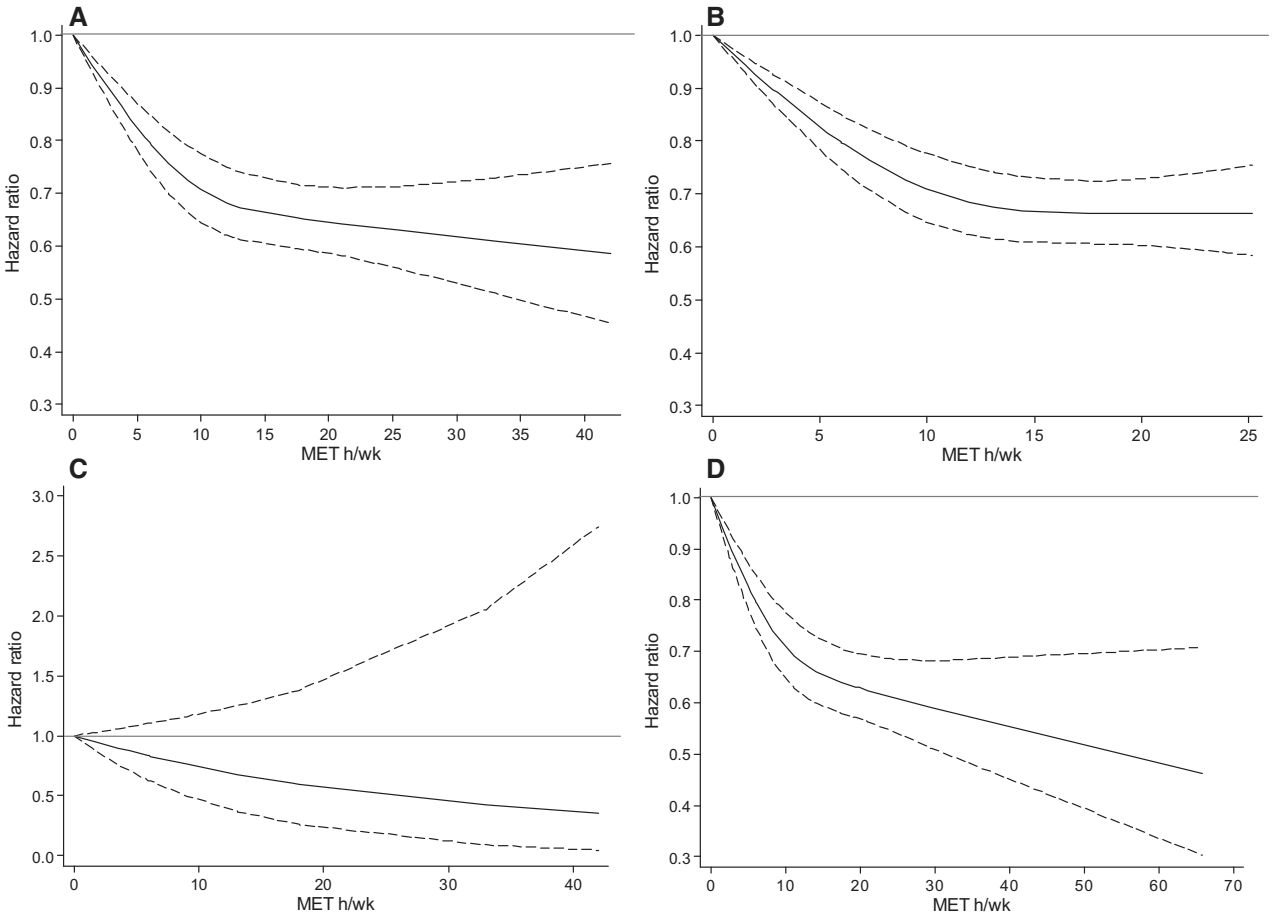

Figure 4. Random-effects dose-response curves for recreational physical activity in breast cancer survivors. **A**) Prediagnosis physical activity and breast cancer-specific mortality (n = 7 sets of data from six studies); **B**) postdiagnosis physical activity and breast cancer-specific mortality (n = 7 sets of data from six studies); **C**) prediagnosis physical activity and all-cause mortality (n = 5 sets of data from four studies); **D**) postdiagnosis physical activity and all-cause mortality (n = 8 sets of data from seven studies). MET = metabolic equivalent.

We were unable to examine the associations between PA and cancer recurrence, progressions, or other cancer outcomes because of the heterogeneous definitions used across the source studies. Likewise, an interest in precision exercise oncology is to examine how cancer population subgroups, defined by clinical or pathologic characteristics, respond to PA (165). To date, few studies have examined these clinicopathologic subgroups to identify which populations might benefit more from PA. With additional research on this topic and the prerequisite that future studies follow standardized definitions of outcomes (eg, STEEP guidelines) and comprehensively report patient and tumor characteristics, analyses by specific outcomes will also be possible and highly informative (166). Finally, future studies are needed that use the highest quality of PA assessment with objective and self-report measures and the reporting in MET hours per week to permit additional evaluations of the dose-response effects in other cancer sites.

In summary, we found strong evidence that PA before or after cancer diagnosis was associated with statistically significant decreased hazards of cancer-specific and all-cause mortality in at least 11 different cancer sites. In addition, we found that hazard of CVD mortality among cancer survivors was also reduced with PA. As such, these findings confirm the importance of promoting PA after cancer and suggest that in doing so, there is huge potential for patient and public health gain through PA.

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CMF, SCH, and CRS designed and conceptualized the study; CRS conducted the literature search and eligibility review, abstracted the study details and results, contacted authors for additional details, conducted the analysis, prepared the tables and figures, and drafted the study methods and results; CMF wrote the final paper with input from SCH and WYC. WYC also provided input on subgroup analyses. All authors reviewed and approved the final draft. The corresponding author had full access

to all the data in the study and had final responsibility for the decision to submit for publication.

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