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
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, 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 pre-diagnosis and post-diagnosis 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/m²), menopausal status, and estimates by colorectal cancer sub-site 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/m², ≥25 kg/m²), 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 I² statistics, which serve to describe the percentage of variation across studies due to heterogeneity rather than chance; I² 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 Beggs 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 in 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,
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 pre-diagnosis 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 post-diagnosis PA were reduced both for men and women (all cancers and within colorectal cancer), those with lower BMI (<25 kg/m²; 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/m² (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        | —               | 11663                  | 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        | —               | 41675                  | 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 | 15001       | —               | 293511                 | 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        | —               | 303428                 | 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 | Prediagnosis | —         | 9                |
| **Studies assessing only all-cancer** |               |             |            |                 |                        |              |                               |               |                  |
| Arraiz, 1992, Canada (34) | Canada Health Survey Mortality Follow-up Study | All | 229         | —               | 12917                  | Cancer-specific | Prediagnosis                  | —             | 9                |
| Kampert, 1996, United States (35) | Aerobics Center Longitudinal Study | All | 223         | —               | 32421                  | Cancer-specific | Prediagnosis                  | No overall, by sex | 7                |

(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 |
| Klander, 2001, Sweden (37)       | — | All | 216 | — | 2285 | Cancer-specific | Prediagnosis | Men only | 8 |
| Hu, 2005, Finland (38)           | Copenhagen City Heart Study | All | 2039 | — | 47212 | Cancer-specific | Prediagnosis | No overall, by sex | 8 |
| Schnohr, 2006, Denmark (39)      | Shanghai Women’s Health Study | All | 632 | — | 4894 | Cancer-specific | Prediagnosis | — | 8 |
| Matthews, 2007, China (40)       | Cohort of Swedish Men | All | 537 | — | 67143 | Cancer-specific | Prediagnosis | Women only | 9 |
| Orsini, 2008, Sweden (41)        | Nurses’ Health Study | All | 901 | — | 37633 | Cancer-specific | Prediagnosis | No overall, by BMI, men only | 8 |
| van Dam, 2008, United States (42)| Scottish Health Surveys | All | 4527 | — | 77782 | Cancer-specific | Prediagnosis | Women only | 7 |
| Hamer, 2009, Scotland (43)       | MONICA/KORA Augsburg Survey S2 | All | 78 | 293 | 293 | All-cause | Prediagnosis | Type of PA | 9 |
| Autenrieth, 2011, Germany (44)   | Norwegian Women and Cancer Cohort Study | All | 326 | — | 4672 | Cancer-specific | Prediagnosis | Type of PA | 9 |
| Borch, 2011, Norway (45)         | Eastern Finnish Follow-up Study | All | 1584 | — | 66136 | Cancer-specific | Prediagnosis | Women only | 8 |
| Laukkanen, 2011, Finland (46)    | Cancer Prevention Study-II Nutrition Cohort | All | 181 | — | 2560 | Cancer-specific | Prediagnosis | Men only | 9 |
| McCullough, 2011, United States (47)| Taichung Diabetes Study | All | 5874 | — | 111966 | Cancer-specific | Prediagnosis | No overall, by sex | 8 |
| Lin, 2012, Taiwan (48)           | Severance Cohort Study | All | 122 | — | 5686 | Cancer-specific | Prediagnosis | — | 8 |
| Mok, 2012, Korea (49)            | Third National Health and Nutrition Examination Survey | All | 1060 | 3555 | 59636 | Cancer-specific | Prediagnosis | No overall, by sex | 8 |
| Parekh, 2012, United States (50) | Iowa Women’s Health Study | All | 860 | — | 15535 | Cancer-specific | Prediagnosis | BMI | 9 |
| Inoue-Choi, 2013, United States (51)| European Prospective Investigation into Cancer and Nutrition | All | 461 | 2017 | 2017 | All-cause, cancer-specific, CVD-specific | Prediagnosis | Women only | 8 |
| Vergnaud, 2013, Europe (52)      | — | All | 9388 | — | 378864 | Cancer-specific | Prediagnosis | Sex | 8 |
| 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       | —              | 61477                 | 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      | Prediagnosis               | —              | 8                    |
| Hastert, 2014, United States (57) | Vitamins and Lifestyle Study | All         | 1595       | —              | 57841                 | Cancer-specific | Prediagnosis               | —              | 8                    |
| Lee, 2014, United States (58)   | Harvard Alumni Health Study | All         | 777        | 1021           | 1021                  | All-cause, cancer-specific, CVD-specific Cancer-specific | Prediagnosis | Men only | 7 |
| Wanner, 2014, Switzerland (59)  | MONICA/National Research Program 1A | All         | 1351       | —              | 17663                 | 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         | 16193      | 73 784         | 476396                | Cancer-specific | Prediagnosis | No overall, by sex | 8 |
| Kraschnewski, 2016, United States (62) | National Health Interview Survey | All         | —          | —              | 30162                 | Cancer-specific | Prediagnosis | — | 7 |
| Lee, 2016, Korea (63)           | Kangbuk Samsung Health Study | All         | 970        | —              | 336560                | Cancer-specific | Prediagnosis | Age, sex, BMI | 8 |
| Robashm, 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 | Prediagnosis | — | 9 |
| Kamada, 2017, United States (66) | Women’s Health Study | All         | 748        | —              | 28879                 | Cancer-specific | Prediagnosis | Women only | 8 |
| O’Donovan, 2017, United Kingdom (67) | Health Survey for England and Scottish Health Survey | All         | 2526       | —              | 63591                 | Cancer-specific | Prediagnosis | — | 9 |

(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 | — | 120727 | Cancer-specific | Prediagnosis | Sex | 9 |
| Patel, 2018, United States (71) | Cancer Prevention Study-II Nutrition Cohort | All | 13186 | — | 139255 | Cancer-specific | Prediagnosis | — | 8 |
| Studies assessing only bladder cancer | | Bladder | 83 | — | 222163 | Cancer-specific | Prediagnosis | — | 9 |
| Liss, 2017, United States (72) | National Health Information Survey | Bladder | 83 | — | 222163 | Cancer-specific | Prediagnosis | — | 9 |
| 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) | Nurses’ Health Study | Breast | 251 | 717 | 717 | Cancer-specific | Prediagnosis | — | 9 |
| Holmes, 2005, United States (76) | | 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 |
| Hollick, 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 |
| Author, year, country | Name of study | Cancer type | No. in analytic sample | No. with cancer | No. deaths | Outcome type | Subgroups used | Physical activity assessment | Quality score |
|-----------------------|---------------|-------------|------------------------|----------------|------------|--------------|----------------|-------------------------------|---------------|
| Emaus, 2010, Norway (84) | Norwegian Counties Heart Study | Breast | 429 | 1364 | 1364 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis | 8 |
| Hellmann, 2010, Denmark (85) | Copenhagen City Heart Study | Breast | 322 | 528 | 528 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis | 8 |
| Keegan, 2010, United States, Canada, Australia (86) | Breast Cancer Family Registry | Breast | 725 | 4153 | 4153 | All-cause | All-cause | Prediagnosis | 8 |
| Bertram, 2011, United States (87) | Women's Healthy Eating and Living Study | Breast | 163 | 2361 | 2361 | All-cause | All-cause | Prediagnosis | 8 |
| Chen, 2011, China (88) | Shanghai Breast Cancer Survival Study | Breast | 350 | 463 | 463 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis, postdiagnosis | 8 |
| Irwin, 2011, United States (89) | Women's Health Initiative | Breast | 1663 | 13202 | 13202 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis, postdiagnosis | 7 |
| Beasley, 2012, United States, China (90) | After Breast Cancer Pooling Project: LACE-NHS-SBCSS-WHEL | Breast | 196 | 1508 | 1508 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis | 9 |
| Cleveland, 2012, United States (91) | Long Island Breast Cancer Study Project | Breast | 367 | 3393 | 3393 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis | 9 |
| Schmidt, 2013, Germany (92) | MARIE Study | Breast | 170 | 1207 | 1207 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis | 9 |
| Tao, 2013, United States (93) | Western New York Exposure and Breast Cancer Study | Breast | 111 | 482 | 79 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis | 9 |
| Williams, 2013, United States (94) | National Runners' and Walkers' Health Survey | Breast | 420 | 1423 | 1423 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis | 7 |
| de Glas, 2014, Netherlands (95) | Tamoxifen Exemestane Adjuvant Multicenter | Breast | 80 | 521 | 521 | All-cause, cancer-specific | All-cause, cancer-specific | Prediagnosis | 6 |
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 | Prediagnosis | — | 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 |
| Parad, 2019, United States (110) | Carolina Breast Cancer Study | Breast | 717 | 1808 | 1808 | All-cause | Prediagnosis | — | 9 |
| Studies assessing only cervical cancer | — | Cervical | 30 | 860 | 860 | All-cause | Postdiagnosis | — | 8 |
| Kim, 2016, Korea (111) | — | — | — | — | — | — | — | — | 8 |
| Studies assessing only childhood cancer | — | Childhood Cancer Survivor Study | Childhood cancer | 1063 | 15450 | 15450 | All-cause, CVD-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) |
|---------------------------------|---------------|-------------|------------|----------------|-----------------------|--------------|-----------------------------|----------------|------------------|
| 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 | — | 539201 | Cancer-specific | Prediagnosis | — | 6 |
| Meyerhardt, 2009, United States (115) | Health Professionals Follow-Up Study | Colorectal | 258 | 668 | 668 | All-cause, cancer-specific | Prediagnosis | 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 | — | 17949 | 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) | Colorectal 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 | — | 226089 | Cancer-specific | Prediagnosis | No overall, by sex, colon vs rectum, age, BMI | 8 |
| 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 |
|---------------------------------|------------------------------------------------------------------------------|-------------------|------------|----------------|------------------------|------------------------|-------------------------------|--------------------------------|---------------|
| 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              | Prediagnosis                | 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             |
| Studies assessing only malignant glioma | Ruden, 2011, United States (135) | —                  | Malignant glioma | 149          | 243                | 243                    | All-cause              | Prediagnosis                | —                           | 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)
| 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) |
|---------------------------------|---------------|-------------|------------|----------------|------------------------|--------------|-----------------------------|---------------|---------------------|
| Schmid, 2018, United States (139) | National Institutes of Health–AARP Diet and Health Study | Kidney | 175 | 667 | 667 | All-cause, cancer-specific | Postdiagnosis | — | 8 |
| 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 |
| Schwitzer, 2017, Australia, Canada, Italy, United States (142) | Genes, Environment and Melanoma Study | Melanoma | 341 | 2465 | 2465 | All-cause, cancer-specific | Prediagnosis | — | 9 |
| 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 |
| Lee, 2003, United States (147) | College Alumni Health Study | Pancreatic | 212 | — | 32687 | Cancer-specific | Prediagnosis | — | 7 |
| Lin, 2007, Japan (148) | Japanese Collaborative Cohort Study | Pancreatic | 402 | — | 100932 | Cancer-specific | Prediagnosis | No overall, by sex | 8 |
| Stevens, 2009, United Kingdom (149) | Million Women Study | Pancreatic | 1710 | — | 1290000 | Cancer-specific | Prediagnosis | Women only | 8 |
| Nakamura, 2011, Japan (150) | Takayama Study | Pancreatic | 52 | — | 30826 | Cancer-specific | Prediagnosis | No overall, by sex | 8 |

(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) |
|---------------------------------|--------------|-------------|------------|----------------|-----------------------|--------------|----------------------------|----------------|-------------------|
| Nilsen, 2006, Norway (151)      | HUNT Study (Norway) | Prostate | 354 | 957 | 29,110 | Cancer-specific | Prediagnosis | — | 8 |
| Crespo, 2008 (152)              | Puerto Rico Heart Health Program | Prostate | 167 | — | 9,780 | 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 | 2,705 | 2,705 | All-cause, cancer-specific | Prediagnosis | — | 7 |
| Bonn, 2015, Sweden (156)        | Progression in Cancer of the Prostate | Prostate | 561 | 4,623 | 4,623 | All-cause, cancer-specific | Prediagnosis | 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 | 7,328 | 7,328 | All-cause, cancer-specific | Prediagnosis, postdiagnosis | — | 8 |

*BMI = body mass index; CRC = colorectal cancer; CVD = cardiovascular disease; PA = physical activity.
all P < .05) compared with those with BMI greater than 25 kg/m² (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...
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.

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 HRs ~ 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 prediagnosis 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/m². Currently, there are insufficient data to support specific recommendations related to

| Cancer site       | No. of studies | No. of estimates | Hazard ratio (95% CI) |
|-------------------|----------------|------------------|----------------------|
| Prediagnosis physical activity |                 |                  |                      |
| All a             | 1              | 1                | 0.47 (0.29 to 0.75)  |
| Breast b          | 19             | 21               | 0.82 (0.76 to 0.87)  |
| Colorectal c      | 10             | 10               | 0.80 (0.74 to 0.87)  |
| Esophagus d       | 1              | 1                | 0.90 (0.50 to 1.50)  |
| Female reproductive e | 5           | 5                | 0.91 (0.79 to 1.05)  |
| Hematologic f     | 3              | 7                | 0.84 (0.79 to 0.89)  |
| Melanoma g        | 2              | 2                | 0.87 (0.67 to 1.14)  |
| Prostate h        | 1              | 1                | 0.89 (0.82 to 0.98)  |
| Stomach i         | 1              | 1                | 0.80 (0.50 to 1.20)  |
| Postdiagnosis physical activity |             |                  |                      |
| All j             | 6              | 6                | 0.61 (0.51 to 0.73)  |
| Breast b          | 17             | 18               | 0.58 (0.52 to 0.65)  |
| Childhood k       | 1              | 1                | 0.79 (0.62 to 1.00)  |
| Colorectal l      | 10             | 10               | 0.63 (0.50 to 0.78)  |
| Esophagus m       | 1              | 1                | 0.96 (0.67 to 1.39)  |
| Female reproductive k | 4          | 4                | 0.66 (0.49 to 0.88)  |
| Glioma n          | 1              | 1                | 0.64 (0.46 to 0.91)  |
| Hematologic o     | 2              | 5                | 0.60 (0.51 to 0.69)  |
| Kidney p          | 1              | 1                | 0.60 (0.38 to 0.95)  |
| Lung q            | 2              | 2                | 0.76 (0.60 to 0.97)  |
| Prostate h        | 5              | 5                | 0.60 (0.46 to 0.79)  |
| Stomach i         | 1              | 1                | 0.75 (0.61 to 0.93)  |

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). *Ref. (60). †Ref. (77,78,80,81,83–86,89,91,92,96,97,100–102,105,108,110). ‡Ref. (113,118–120,122–124,128–130). ‡Ref. (112). §Ref. (33,134,135). ‡Ref. (139). †Ref. (140,141). ‡Ref. (139). ‡Ref. (140,141). ‡Ref. (139). ‡Ref. (140,141). ‡Ref. (139). ‡Ref. (33,155–157,159). ‡Ref. (30). CI = confidence interval.
Table 2. Subgroup meta-analyses of the association between physical activity and cancer mortality, separately by sex, BMI, menopausal status, and colorectal subsite*  

| Subgroup | Prediagnosis physical activity | Postdiagnosis physical activity |
|----------|--------------------------------|---------------------------------|
|          | No. of studies/No. of estimates | HR (95% CI) | P | I² | No. of studies/No. of estimates | HR (95% CI) | P | I² |
| 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/m²) | 3/3 | 0.77 (0.62 to 0.96) | .018 | 0.00% | – | – | – | – |
| All cancers (≥25 kg/m²) | 2/2 | 0.91 (0.66 to 1.25) | .568 | 0.00% | – | – | – | – |
| Breast (<25 kg/m²) | 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/m²) | 4/4 | 0.76 (0.48 to 1.22) | .258 | 73.40% | 7/8 | 0.61 (0.30 to 0.75) | <.001 | 50.20% |
| Colorectal (<25 kg/m²) | 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/m²) | 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/m²) | 1/1 | 1.07 (0.55 to 2.11) | .844 | – | – | – | – | – |
| Prostate (≥25 kg/m²) | 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/m²) | 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/m²) | 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/m²) | 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/m²) | 2/2 | 0.73 (0.58 to 0.92) | .009 | 0.00% | 2/3 | 0.71 (0.47 to 1.18) | .112 | 38.60% |
| Hematologic (<25 kg/m²) | 1/1 | 0.80 (0.67 to 0.96) | .015 | – | 1/1 | 0.54 (0.36 to 0.79) | .002 | – |
| Hematologic (≥25 kg/m²) | 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.

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 0.46 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, colorectal, prostate, and hematologic), the magnitude of the effect of PA on cancer-specific and all-cause mortality outcomes was greater than 0.60, indicating a stronger association.
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.

### 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     | I²   | No. of studies/No. of estimates | HR (95% CI) | P     | I²   |
|--------------------|-------------|---------------------------------|-------------|-------|------|---------------------------------|-------------|-------|------|
| 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) |       |        |       |                       |       |       |
|                    | Total Breast   | 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 |        |       |                       |       |       |
|                    | Total Colorectal | 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      |       |                       |       |        |       |                       |       |       |
|                    | Total Prostate  | 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  |       |                       |       |        |       |                       |       |       |
|                    | 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 |       |
|                    | Total Breast   | 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 |       |
|                    | Total Colorectal | 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   | 2/2   | 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.
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.
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