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The dose–response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies

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ABSTRACT

Background The WHO recommends moderate physical activity to combat the increasing risk of death from chronic diseases. We conducted a meta-analysis to assess the association between physical activity and cancer mortality and the WHO recommendations to reduce the latter.

Methods MEDLINE and EMBASE were searched up until May 2014 for cohort studies examining physical activity and cancer mortality in the general population and cancer survivors. Combined HRs were estimated using fixed-effect or random-effect meta-analysis of binary analysis. Associated HRs with defined increments and recommended levels of recreational physical activity were estimated by two-stage random-effects dose–response meta-analysis.

Results A total of 71 cohort studies met the inclusion criteria and were analysed. Binary analyses determined that individuals who participated in the most physical activity had an HR of 0.83 (95% CI 0.79 to 0.87) and 0.78 (95% CI 0.74 to 0.84) for cancer mortality in the general population and among cancer survivors, respectively. There was an inverse non-linear dose–response between the effects of physical activity and cancer mortality. In the general population, a minimum of 2.5 h/week of moderate-intensity activity led to a significant 13% reduction in cancer mortality. Cancer survivors who completed 15 metabolic equivalents of task (MET)-h/week of physical activity had a 27% lower risk of cancer mortality. A greater protective effect occurred in cancer survivors undertaking physical activity postdiagnosis versus prediagnosis, where 15 MET-h/week decreased the risk by 35% and 21%, respectively.

Conclusions Our meta-analysis supports that current physical activity recommendations from WHO reduce cancer mortality in both the general population and cancer survivors. We infer that physical activity after a cancer diagnosis may result in significant protection among cancer survivors.

INTRODUCTION

Cancer is a leading disease burden in developed and developing countries with 8.2 million cancer deaths in 2012 as estimated by the WHO.[1] The World Cancer Research Fund (WCRF) recently reaffirmed that the risk of cancer is affected by our lifestyles and that an active lifestyle is protective against cancer mortality.[2] Specifically, an inverse association between physical activity and mortality has been discovered for breast,[3] colorectal[4] and prostate cancers.[5] The association was further validated by meta-analyses in breast and colorectal cancers.[6 7] However, the magnitude and intensity of physical activity most beneficial against cancer mortality is unclear. The most recent guidelines promoted by the WHO recommend a minimum of 2.5 h of moderate intensity physical activity (3 to <6 metabolic equivalents of task (MET)) or 1.25 h of vigorous intensity physical activity (≥6 METs) per week or any equivalent combination for health benefits, and 5.0 h of moderate intensity physical activity or 2.5 h of vigorous intensity physical activity per week for additional health benefits.[8–11] Specific recommendations to prevent cancer mortality are still lacking.[12] Accordingly, we conducted a meta-analysis of prospective studies to assess the association of physical activity with cancer mortality and to explore whether the current WHO recommendations are optimal.

METHODS

Search strategy and study selection

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] MEDLINE and EMBASE databases were searched up to 30 May 2014 for cohort studies published in English that investigated the association between physical activity and cancer mortality. The search terms were as follows: ('exercise', 'physical activity', 'walking' or 'motor activity' with 'cancer', 'neoplasm' or 'carcinoma'). Duplicate studies were removed, and the reference lists of relevant literature and previous relevant reviews and meta-analyses were checked for additional publications of interest.

Included studies fulfilled the following criteria: (1) cohort study design, (2) physical activity (eg, leisure-time physical activity, recreational physical activity, exercise and sports, routine activity of daily living, physical activity of transportation, etc) included as a variable, (3) investigated the association between physical activity and cancer mortality (defined as deaths due to cancer) in the general population or among cancer survivors and (4) provided relative risk (RR) or HR estimates and 95% CIs or sufficient data to calculate them. Studies were excluded if they: (1) studied a population with a chronic disease (eg, cardiovascular disease or diabetes mellitus), (2) measured physical fitness but not physical activity, (3) focused on cancer risk not cancer mortality or (4) measured only work-related physical activity. Two authors independently read the full text of all included articles to determine whether each study met the eligibility criteria outlined above.

Data extraction

Data collection and extraction were conducted independently by two investigators, and all discordances were resolved by discussion. For each study, the following information was extracted: first author's name, publication year, cohort name, study location, study design, age at baseline, gender, number of cases or participants, number of cancer deaths, domains of physical activity, when physical activity was measured (prediagnosis (in the general population study), prediagnosis or postdiagnosis (in the cancer survival study)), amounts of physical activity at each level in different units (eg, MET-h/week, h/week, kcal/week and km/h), cancer type, duration of follow-up, estimate of effect (reported as a RR, HR) and the corresponding 95% CI for the association of physical activity with cancer mortality, and adjustment variables (eg, age, body mass index (BMI) and stage). We extracted the binary estimate of the most comprehensive domain of physical activity from each study for a pooled assessment of the most active group compared with the least active group. The effect and 95% CI were inverted for study in which the most active group was used as the reference group. Estimates from each level of recreational physical activity, the most commonly measured domain and main modifiable form of energy expenditure, were extracted for dose–response analysis.[14] Lifetime results were used if a study reported the effect of physical activity at both multiple ages and over a lifetime. When a study reported separately on males and females, both risk estimates were included in the primary analysis. Additionally, in the case of multiple publications, we included the most up-to-date or comprehensive information.

Assessment of risk of bias in individual studies

We used the Newcastle-Ottawa quality assessment scale[15] to assess the risk of bias in each individual study based on the following: representativeness of the exposed cohort, selection of the unexposed cohort, methods of measuring physical activity, comparability of cohorts based on design or analysis, adjustment for confounding factors (age, BMI, stage, tumour differentiation, etc), duration and adequacy of follow-up, and study end points (cancer mortality). High-quality responses earned a star with up to nine stars in total.

Statistical analysis

Binary analysis, and fixed-effect or random-effect models were used to estimate the summary HRs for associations between physical activity and cancer mortality when appropriate.[16] Dose–response analyses were conducted for studies with three or more quantitative activity levels in MET-h/week and h/week, the most applicable measures of physical activity, using non-linear random effect models.[17] For each activity level, the median or mean amount of physical activity was assigned to the corresponding HR estimate. If the median or mean value was not reported, we used the midpoint of the upper and lower boundaries of each category. For studies reporting open upper boundaries for the highest category (eg, >200 min/week), we multiplied the reported lower boundary by 1.25 and used this value (eg, 250 min/week) as the midpoint.[18] Heterogeneity in the relationship between physical activity and cancer mortality was assessed by Q test and quantified by I^2 statistic.[19] In order to assess the effect of the study characteristics and quality on the reported estimates, heterogeneity was analysed by comparing the effect estimate summary from subgroup analyses. Subgroup analyses were conducted in topics that had at least three original studies and were by cancer type, gender, study location, follow-up duration (<10 years, ≥10 years) and when physical activity was measured (prediagnosis or postdiagnosis). To test for statistically significant potential confounders (eg, publication year, study location, follow-up duration, cancer type, when physical activity was measured, measurement of physical activity, study design and quality), meta-regression analysis[20] was used to calculate ratios of risk. Publication bias was examined using Begg's test and Egger's test.[21] We performed sensitivity analyses by omitting one study at a time from the initial meta-analysis. All statistical tests were two-sided and p values <0.05 were considered statistically significant. All analyses were conducted using Stata software (V.12.0; StataCorp, College Station, Texas, USA).

RESULTS

Study selection

In total, 16 980 articles were initially identified in the literature search; and 10 619 articles were left after removing duplicates, of which 10 422 studies were not relevant to the main topic and excluded. Thirty of the remaining 197 studies were excluded due to a focus on occupational physical activity, 91 for not fulfilling the inclusion criteria and 7 for providing information from overlapping studies. Two additional articles were identified in a manual search of reference lists. Overall, 71 studies were included in the primary meta-analysis (figure 1).

Characteristics of the studies

Of the 71 prospective studies reporting on the association between physical activity and cancer mortality, 36 were general population-based studies[S[1–36]] and 35 studies were conducted among cancer survivors.[S[37–71]] The major characteristics of these studies and reference list are shown in online supplementary table S1. In total, 3 985 164 participants were included in the general population-based studies and 66 995 cancer deaths were observed. Nine studies were done in North

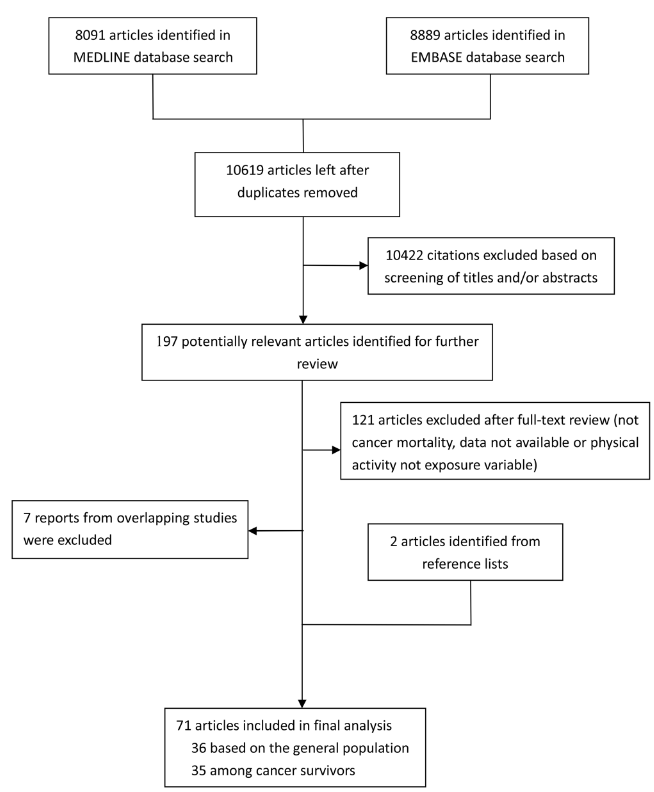

Figure 1 Flow diagram of study selection.

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America,[S1 2 8 16 23 28 32 34 35] 9 in Asia[S7 12–14 25–27 31 33] and 18 in Europe.[S3–6 9–11 15 17–22 24 29 30 36] Twenty-two studies provided data on the relationship between physical activity and mortality from various cancer,[S1–6 9 11 14–16 19 21–23 26 29–31 33 35 36] with five on colorectal cancer,[S12 24 26 27 34] four on pancreatic cancer[S8 13 18 25] and three on breast cancer.[S26 32 34] In the 35 cancer survival studies, 69 011 patients with cancer were included with 9516 cancer deaths. Twenty-five of these studies were conducted in North America,[S38–41 43 44 48–52 54 57–65 68–71] and six in Europe.[S45–47 53 55 67] Nineteen studies were on breast cancer survival[S37–41 44 47 50–55 57 60 61 67–69] and nine on colorectal cancer survival.[S42 43 49 56 59 62 65 66 70] Of these, 24 studies,[S37–43 45–47 51 53–55 57 61–65 67 68 70 71] 14 studies[S40 43 44 49 50 56–60 62 65 66 69] and five studies[S40 43 57 62 65] reported on the association between prediagnosis, postdiagnostic or both prediagnostic and postdiagnostic physical activity, respectively, and cancer mortality. The overall quality score ranged from 6 to 9 based on the Newcastle-Ottawa scale with 16 studies scoring 6 stars, 10 scoring 9 stars and the rest 7–8 stars.

The role of physical activity in reducing cancer mortality in the general population

Binary analysis

As shown in table 1, compared to the lowest amount of physical activity, the highest amount of physical activity presented significant protection against death from cancer, with a pooled HR of 0.83 (95% CI 0.79 to 0.87, I^2=65.6%). Consistent associations were confirmed by subanalyses of gender, study location, duration of follow-up and cancer type. The highest levels of physical activity reduced cancer mortality by 17% in males and females. Similarly, studies conducted in North America, Europe and Asia found a 17–19% protective effect. Cancer mortality presented a 17% and 16% reduction in studies, respectively, with a follow-up of less than or at least 10 years. Besides, high level of physical activity reduced the mortality of colorectal cancer by 21%. The heterogeneity of binary comparison was significant (I^2=65.6%), which, based on subgroup analysis, was mainly from North American studies. Besides study location, meta-regression did not find new sources of heterogeneity. Begg's test (p=0.32) and Egger's test (p=0.09) indicated no evidence for publication bias. Also, sensitivity analysis found that the pooled results did not overtly change even on omission of the most influential study (online supplementary figures S1 and S2).

Table 1 Pooled measures on the relation of physical activity to cancer mortality in the general population

	Number of data sets included	HR (95% CI)	I^2 (%)	p Value
Overall	54	0.83 (0.79 to 0.87)	65.6	<0.001
Sex				
Male	22	0.83 (0.75 to 0.92)	71.0	<0.001
Female	14	0.83 (0.73 to 0.94)	67.9	<0.001
Study location				
North America	11	0.83 (0.74 to 0.93)	80.5	<0.001
Europe	24	0.82 (0.75 to 0.90)	69.3	<0.001
Asia	19	0.81 (0.76 to 0.85)	0.0	0.462
Duration of follow-up (year)				
<10	23	0.83 (0.76 to 0.92)	62.6	<0.001
≥10	29	0.84 (0.79 to 0.89)	66.2	<0.001
Cancer types				
Colorectal cancer	6	0.79 (0.71 to 0.88)	0.00	0.477

p Value of Q-test for heterogeneity test.

Dose–response analysis

Figure 2 shows evidence of a non-linear association between recreational physical activity and cancer mortality by MET-h/week in general population. The HRs of cancer mortality following 5, 10, 15, 20 and 25 MET-h/week of recreational physical activity were 0.88, 0.86, 0.86, 0.85 and 0.84, respectively, when compared with inactivity. The dose–response curve steeply sloped below 7.5 MET-h/week, the minimum energy expenditure of 2.5 h moderate physical activity per week recommended by the WHO, and then gently declined. Individuals who met the lower limit of the WHO guidelines, 7.5 MET-h/week, had a 14% lower risk of cancer mortality. An approximate 2% reduction in cancer mortality for every 1 MET-h/week increase below 7.5 MET-h/week occurred compared to a 1% reduction in cancer mortality by every 10 over 7.5 MET-h/week. Pooled results indicate a similar inverse relation between recreational physical activity and cancer mortality in Asians (online supplementary table S2 and figure S3). The HRs of cancer death for 5, 10, 15, 20 and 25 MET-h/week of recreational physical activity were 0.91, 0.87, 0.86, 0.85 and 0.84, respectively, when compared with the lowest amount of physical activity in the Asian population. This curve shows a significant reduction below 12 MET-h/week and over 22 MET-h/week with a 1% reduction in cancer mortality for every 1 MET-h/week. A similar relationship was observed in studies within 10 years of follow-up. Other subgroups could not be analysed due to insufficient data.

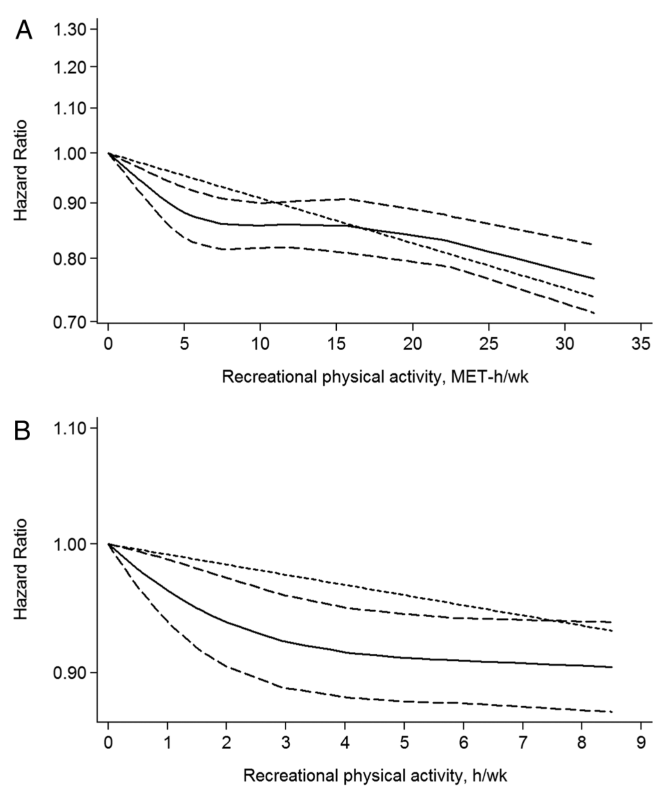

Figure 2 Dose–response relation between cancer mortality and recreational physical activity in the form of metabolic equivalents of task (MET)-h/week (A) and h/week (B) in the general population. The solid line and the long dash line represent the estimated relative risk and its 95% CI. The short dash line represents the linear relationship.

The HRs of cancer mortality for 2, 3, 4, 6 and 8 h/week of recreational physical activity were 0.94, 0.92, 0.91, 0.91 and 0.90, respectively, compared to inactivity (online supplementary table S2). As shown in figure 2, the curve trended a decline with continuously increasing levels of recreational physical activity. Individuals who engaged in 2.5 h/week of recreational physical activity compared to none had a 7% lower cancer mortality. A further 2% reduction in cancer mortality was seen for every additional 6 h/week activity over 2.5 h/week. Subgroup analyses are presented in online supplementary figure S3. Cancer mortality decreased rapidly below 2 h/week and then declined steadily over 2 h/week in North Americans. A similar effect was observed in individuals following up over 10 years. Other subgroups could not be analysed due to insufficient data.

The role of physical activity in reducing cancer mortality in cancer survivors

Binary analysis

A strong association between high levels of physical activity and cancer mortality was observed in cancer survivors with an HR of 0.78 (95% CI 0.72 to 0.84, I^2=56.9%) (table 2). The highest levels of physical activity reduced cancer mortality by 21% in female cancer survivors. However, we did not observe a similar association in males. The protection by physical activity against cancer death was further observed in North American studies with reduced 25% cancer mortality, but not in European. The association between physical activity and cancer mortality was not affected by duration of follow-up, which showed a 20% and 30% lower risk in participants followed up for less than and at least 10 years, respectively. A more pronounced protection from postdiagnostic physical activity (HR=0.60, 95% CI 0.50 to 0.71, I^2=53.8%) than prediagnostic physical activity (HR=0.86, 95% CI 0.80 to 0.92, I^2=16.7%) was observed among cancer survivors. This inverse association between physical activity and cancer mortality was confirmed in breast cancer survivors and colorectal cancer survivors. There was evidence of heterogeneity between cancer survival studies of highest versus lowest levels of physical activity (I^2=56.9%). On the basis of subgroup analyses, the studies conducted in North America are responsible for most of the observed heterogeneity. Meta-regression analysis indicated that how physical activity was measured (p=0.01) was statistically significant in a multivariate model, while Egger's test suggests publication bias (p<0.001). Results from the sensitivity analysis did not change even if the most influential study was omitted (online supplementary figures S1 and S2).

Table 2 Pooled measures on the relation of physical activity to cancer mortality among cancer survivors

	Number of data sets included	HR (95% CI)	I^2 (%)	p Value
Overall	57	0.78 (0.72 to 0.84)	56.9	<0.001
Sex				
Female	43	0.79 (0.74 to 0.84)	37.0	0.009
Male	3	0.80 (0.57 to 1.12)	79.2	0.008
Study location				
North America	45	0.75 (0.68 to 0.82)	63.2	<0.001
Europe	8	0.90 (0.78 to 1.02)	0.0	0.679
Duration of follow-up (year)				
<10	45	0.80 (0.74 to 0.87)	51.6	<0.001
≥10	11	0.70 (0.55 to 0.88)	60.7	0.005
Cancer types				
Breast cancer	33	0.76 (0.70 to 0.82)	30.2	0.053
Colorectal cancer	14	0.76 (0.64 to 0.90)	50.7	0.015
When physical activity was measured				
Prediagnosis	34	0.86 (0.80 to 0.92)	16.7	0.198
Postdiagnosis	16	0.60 (0.50 to 0.71)	53.8	0.006

p Value of Q-test for heterogeneity test.

Dose–response analysis

The pooled results show the expected inverse relationship between recreational physical activity and cancer mortality. The cancer mortality declined rapidly with a 2% reduction for every 1 MET-h/week below 10 MET-h/week followed by a plateau over 15 MET-h/week (figure 3). Compared with no recreational physical activity, 5, 10, 15, 30 and 50 MET-h/week reduced the overall cancer mortality by 18%, 25%, 27% 30% and 35%, respectively. Subgroup analyses demonstrated that similar trends occurred in all studies included (online supplementary table S3 and figure S4). An inverse association between recreational physical activity and cancer mortality was found in females. The cancer mortality dropped rapidly with a 2% reduction for each added 1 MET-h/week below 10 MET-h/week and then stabilised at 70% for activity over 15 MET-h/week. Similarly, a protective role for recreational physical activity was observed in North Americans and cancer survivors within 10 years of follow-up. In particular, stronger protection occurred against cancer mortality with postdiagnostic physical activity compared with prediagnostic physical activity. Cancer mortality quickly decreased by 35% when individuals participated in 15 MET-h/week of recreational physical activity after diagnosis and a further 5% reduction in cancer mortality occurred with every additional 10 MET-h/week. In comparison, the cancer mortality decreased by 21% at 15 MET-h/week of prediagnostic physical activity with no further reduction on increasing the amount of recreational physical activity (figure 4). We further explored the association between recreational physical activity and breast cancer mortality and the results were similar to the analysis of the female subgroup; the results stabilised at a 2.5% reduction in cancer mortality for every additional 1 MET-h/week below 10 MET-h/week. An inverse linear relationship was found between recreational physical activity and colorectal cancer mortality ($p_{\text{for non-linearity}}$=0.772), which was statistically significant over 10 MET-h/week with a 1% reduction in cancer mortality with every additional 1 MET-h/week online

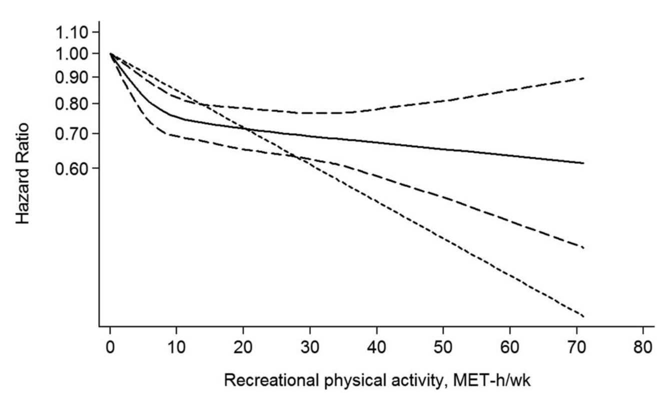

Figure 3 Dose–response relation between cancer mortality and recreational physical activity (metabolic equivalents of task (MET)-h/week) among cancer survivors. The solid line and the long dash line represent the estimated relative risk and its 95% CI. The short dash line represents the linear relationship.

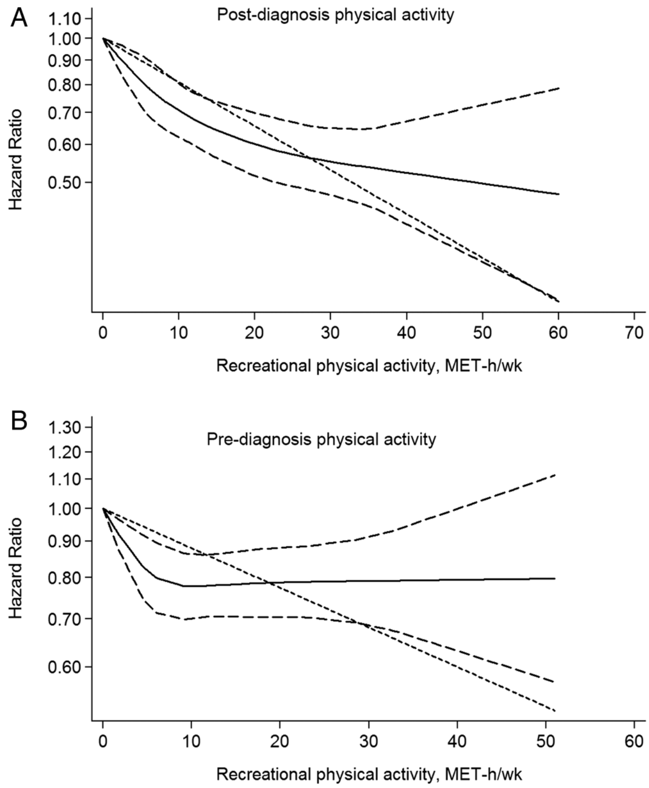

Figure 4 Dose–response relation between cancer mortality and recreational physical activity (metabolic equivalents of task (MET)-h/week) in postdiagnosis (A) and prediagnosis (B) among cancer survivors. The solid line and the long dash line represent the estimated relative risk and its 95% CI. The short dash line represents the linear relationship.

supplementary figure S4. Furthermore, we conducted subset analysis among breast cancer survivors, and a more pronounced benefit was found from postdiagnostic physical activity than prediagnostic physical activity. Compared with no recreational physical activity, 5, 10, 15 and 20 MET-h/week of prediagnostic physical activity reduced breast cancer mortality by 24%, 28%, 29% and 30%, respectively. Meanwhile, breast cancer mortality reduced by 24%, 32%, 39% and 40% when individuals participated in 5, 10, 15 and 20 MET-h/week of recreational physical activity after diagnosis, respectively. Similarly, the decreasing trend in colorectal cancer mortality occurred in postdiagnostic physical activity as in overall physical activity (online supplementary figure S5).

DISCUSSION

This relatively large meta-analysis summarises the contribution of physical activity to reducing cancer mortality and quantifies the reduction in cancer mortality with incremental increases in recreational physical activity. In summary, we found that a high level of physical activity lowered the risk of cancer mortality in the general population and cancer survivors compared to inactivity. Dose–response analyses estimated the benefits for different levels of recreational physical activity by measuring MET-h/week and h/week. The results primarily showed consistent non-linear relationships between recreational physical activity and cancer mortality in the general population and among cancer survivors.

Our findings based on the general population showed that individuals undergoing the highest levels of physical activity had a 17% reduction in cancer mortality. This effect was not influenced by gender, study location or duration of follow-up. Dose–response analyses further revealed that the cancer mortality decreased significantly by 13% and 7% in the general population that undertook 7.5 MET-h/week and 2.5 h/week recreational physical activity, respectively. Recent meta-analyses confirmed a similar inverse relationship between high levels of physical activity and all-cause mortality.[18 22] In particular, one meta-analysis quantified the dose–response of all-cause mortality to non-vigorous physical activity and demonstrated that adhering to the WHO's recommendations contributed to a 19% reduction.[22] A recent dose–response analysis based on six studies from the National Cancer Institution Cohort Consortium found that compared with individuals reporting no leisure time physical activity, 21% lower cancer mortality was steadily observed among those performing 1–3 times of the WHO's recommendation (7.5 to <22.5 MET-h/week).[23] Similarly, our study, based on extensive original publications, confirmed that moderate intensity activity was associated with cancer mortality benefit in the general population as well.

The inverse relationship between physical activity and cancer mortality was also confirmed in cancer survivors. Basically, cancer survivors undertaking the highest level of physical activity had a 22% reduction in cancer mortality. In particular, evidence from the meta-analysis suggests a non-linear dose–response of cancer mortality to recreational physical activity. Our findings confirmed and extend previous qualitative evidence,[6 7] which reported a correlation between physical activity and cancer mortality in breast and colorectal cancers, respectively. In addition, our findings are consistent with recent published quantitative meta-analysis by Zhong *et al*,[24] which revealed a similar non-linear dose–response relationship between physical activity and breast cancer mortality. The effect of recreational physical activity within a female subgroup analysis was very similar to that within the breast cancer subgroup, which suggests that they came out of similar data sources. The benefit of recreational physical activity was evident for North Americans and strongly supports the 2008 Physical Activity Guidelines for Americans, which endorses 2.5 h/week of moderate activity.[25]

Several mechanisms potentially explain the protection afforded by physical activity against cancer mortality. Studies cite the metabolic effects of high physical activity, including lower BMI, lower sex hormones, reduced adiposity, insulin and c-peptide levels and possibly effects on inflammation or the immune system.[26–29] However, the proposed mechanisms may differ based on the type of cancer. For instance, physical activity increases insulin sensitivity.[30] Higher circulating insulin and insulin-like growth factor-1 and lower insulin-binding protein level have been associated with colorectal risk in epidemiology studies.[31–33] A previous study showed higher colorectal cancer mortality among individuals with metabolic abnormalities related to insulin metabolism compared with those without hyperinsulinaemia and insulin resistance.[34] In a similar way, insulin resistance may influence the risk of breast cancer recurrence and mortality,[35] and physical activity is known to lower insulin levels and improve insulin sensitivity.[36 37] Furthermore, exercise intervention studies have measured improvements in insulin-like growth factor 1 (IGF-I) and insulin-like growth factor binding protein 3 (IGFBP-3) and biomarkers related to cancer progression and recurrence among breast cancer survivors following high levels of exercise.[38 39]

Interestingly, we found that the inverse association between physical activity and cancer mortality was more pronounced in postdiagnostic physical activity than prediagnostic physical activity with a 26% difference. Previous meta-analyses conducted in breast and colorectal cancer survival studies clearly supported that postdiagnosis physical activity was associated with lower cancer mortality than prediagnosis physical activity.[7 40] The finding was also supported by a recently published dose–response meta-analysis in breast cancer.[23] On the basis of the studies described above, there is convincing evidence that recreational physical activity after diagnosis is slightly more beneficial against cancer mortality. A possibility is that individuals who participate in physical activity after a cancer diagnosis may be motivated to change their behaviour and adopt a healthier lifestyle following a cancer diagnosis.[41] Furthermore, a longitudinal study focusing on breast cancer and changes in physical activity before and after diagnosis showed that women who increased physical activity to 9 or more MET-h/week after diagnosis had lower mortality due to breast cancer even if they were inactive before diagnosis,[42] and encouraged women diagnosed with breast cancer to initiate and maintain a programme of physical activity. Systematic reviews in randomised controlled trials[43 44] and reviews[45–47] have concluded that physical activity interventions during and after cancer therapies often result in meaningful and reliable improvements in several supportive care outcomes. These benefits include observed changes in physiological measures, objective performance indicators, self-reported functioning and symptoms, psychological well-being and overall quality of life. These findings may prompt the importance of participating in physical activity, especially after a cancer diagnosis, to gain maximum survival benefits.

Strengths of the meta-analysis

This is a large-scale meta-analysis based on 71 prospective studies. The comprehensiveness of our study is its primary strength. Besides, we provide quantified binary assessments, as well as dose–response relationships between recreational physical activity and cancer mortality. Overall, our results clarify and provide evidence for the WHO guidelines on physical activity at preventing cancer mortality for the general population and also cancer survivors. Our stratified results in the general population study further strengthen our finding by indicating consistent benefits of physical activity in different genders, study locations and durations of follow-up. In addition, we examined the difference between postdiagnostic and prediagnostic physical activity in relation to cancer mortality among cancer survivors in order to better understand the protection against cancer mortality by physical activity at different time points. Various comparisons were conducted to assess the association between physical activity and cancer mortality.

Limitations of the meta-analysis

This meta-analysis has several limitations. First, despite the inclusion of 71 studies in our meta-analysis, we were unable to assess whether the association between physical activity and cancer mortality differed by race, age or cancer type due to insufficient variation among studies in dose–response analyses. In this meta-analysis, the dose–response associations were only explored in subgroup analyses of female, North America, and breast and colorectal cancers. Second, there was significant heterogeneity for several outcomes that could not be explained by geography. The methods of how physical activity was assessed also contributed as physical activity is a complex behaviour with many components, and therefore it is difficult to accurately measure and classify the type of physical activity and its characteristics (ie, intensity, duration and frequency). Third, conclusion related to the associations between high levels of physical activity and cancer mortality in dose–response analyses should be interpreted with caution, especially in the association curve with an upward tail due to the incomplete extreme value (online supplementary figure S6), even though the the tail of the curve became flattened after omitting outliers. Furthermore, a large portion of the physical activity was self-reported; therefore, some misclassification of activity level was probable and quantitative characterisations should therefore be considered approximate in nature. Moreover, for postdiagnostic physical activity, it is possible that the sickest patients are the ones who are unable to exercise and more likely to die. However, to minimise the possibility of survival bias, the original studies conducted by Meyerhardt *et al*[41 48] and Irwin *et al*[42] excluded patients with cancer who either died or recurred within 1 or 2 years of physical activity assessment in their analyses, and the results were not materially altered by that procedure. Besides, all reported outcomes for postdiagnostic physical activity in this meta-analysis have been adjusted for known prognostic variables such as age and stage to reduce the influence of survival bias. Although we used adjusted estimates from included prospective studies, we cannot totally rule out potential residual confounding or confounding by unmeasured factors, such as information on treatment and more details of tumour characteristics, and those unaccounted factors may have an influence on the final results. Finally, our study suggests associations, rather than cause and effect, because of the observational nature of data.

CONCLUSION

In summary, this systematic review and meta-analysis suggests an inverse association between physical activity and cancer mortality. Quantitative data concerning the general population supports the current recommendation of physical activity equivalent to 2.5 h/week of moderate-intensity (3–6 MET-h/week), which could have substantial health benefits for individuals. We also found that a minimum 2.5 h/week of moderate-intensity recreational physical activity conferred protection against cancer mortality among cancer survivors. Therefore, we conclude that the current recommendations concerning physical activity are generally sufficient for reducing cancer mortality. Furthermore, our study displays that physical activity performed before or after cancer diagnosis is related to reduced mortality among cancer survivors. Thus, we infer that

What are the new findings?

- By this meta-analysis based on 71 prospective studies, binary analyses determined that individuals who participated in the most physical activity had an HR of 0.83 (95% CI 0.79 to 0.87) and 0.78 (95% CI 0.74 to 0.84) for cancer mortality in the general population and among cancer survivors, respectively.
- Pooled results indicate the expected inverse non-linear dose–response relationship between recreational physical activity and cancer mortality.
- Our meta-analysis supports that the current recommendation of physical activity (equivalent to 2.5 h/week of moderate intensity) reduces cancer mortality in both the general population and cancer survivors. We infer that physical activity after a cancer diagnosis may result in significant protection among cancer survivors.

How might it impact on clinical practice in the future?

- Our results might be helpful to inform updates on recommendation concerning the advisable amount of physical activity to reduce cancer mortality in the general population and among cancer survivors.
- Future randomised controlled trials could be conducted to verify the role of physical activity in improving cancer mortality.
- Physical activity after diagnosis presents significant protection against cancer mortality. Therefore, physicians may consider to adopt physical active into the clinical practice of cancer treatments.

physical activity after a cancer diagnosis may result in significant protection among cancer survivors. Future randomised controlled trials are needed to verify the role of physical activity in patients with cancer. More high-quality studies are required to clarify the biological mechanisms underlying this association between physical activity and lower cancer mortality.

Contributors TL, SW (Shaozhong Wei) and LL were involved in the design of the study; TL, YS, SP, QQ, JY, YD and QC acquired data from selected studies; all authors were involved in the analysis and interpretation of the data; TL, SW (Shaozhong Wei), and LL drafted the manuscript; all authors provided critical revision of the manuscript for important intellectual content; TL, YS, SP, SW (Sheng Wei) and SN carried out the statistical analyses. All authors read and approved the manuscript. LL and TL had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. SN and LL are the guarantors.

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Competing interests None declared.

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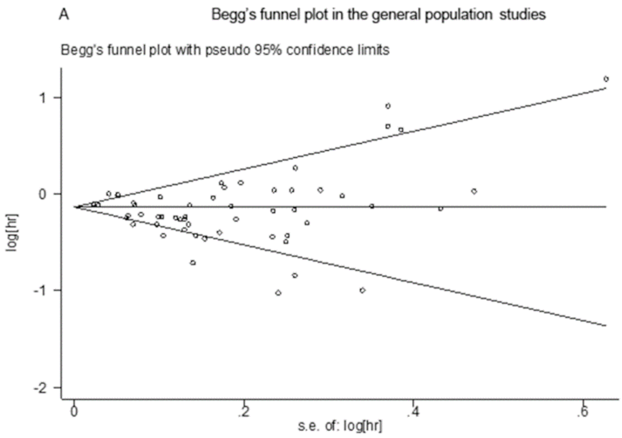
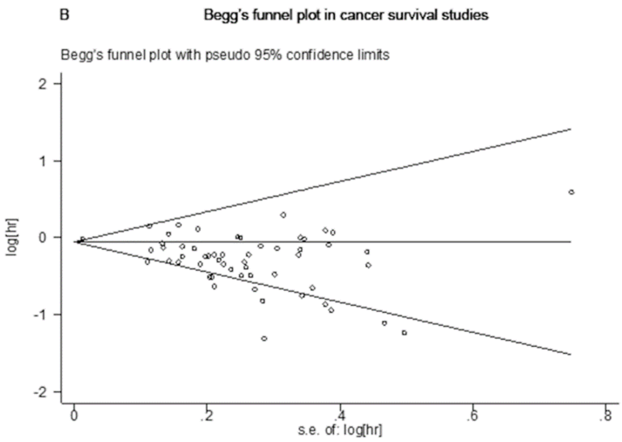
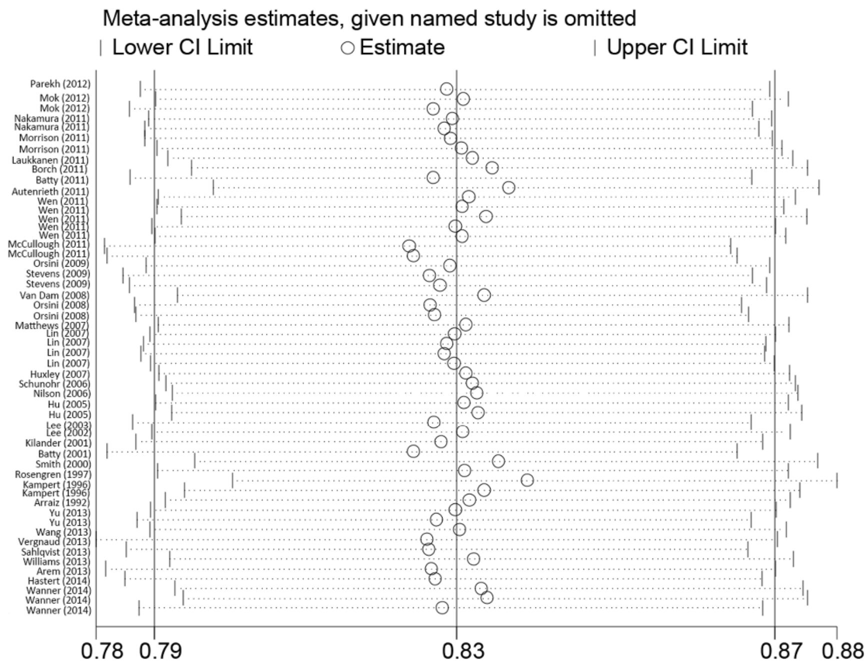
Supplementary figure S1 Begg’s funnel plots of the association between physical activity and cancer mortality in the general population studies (A), and in cancer survival studies (B). The horizontal line is drawn at the pooled log HR. Diagonal lines indicate the pseudo 95% confidence interval.



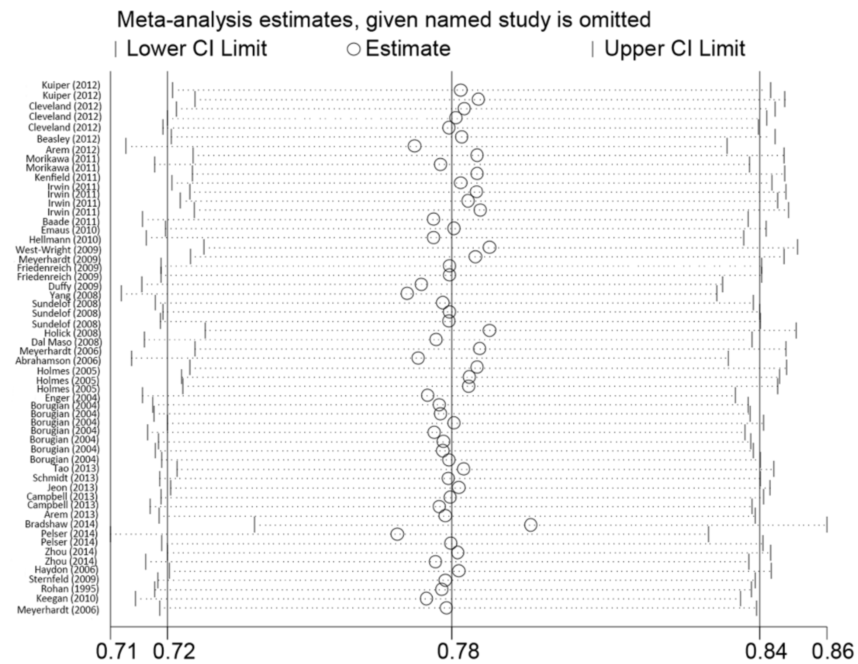


Supplementary figure S2 Sensitivity analyses for the association between physical activity and cancer mortality in the general population studies (A) and in cancer survival studies (B).

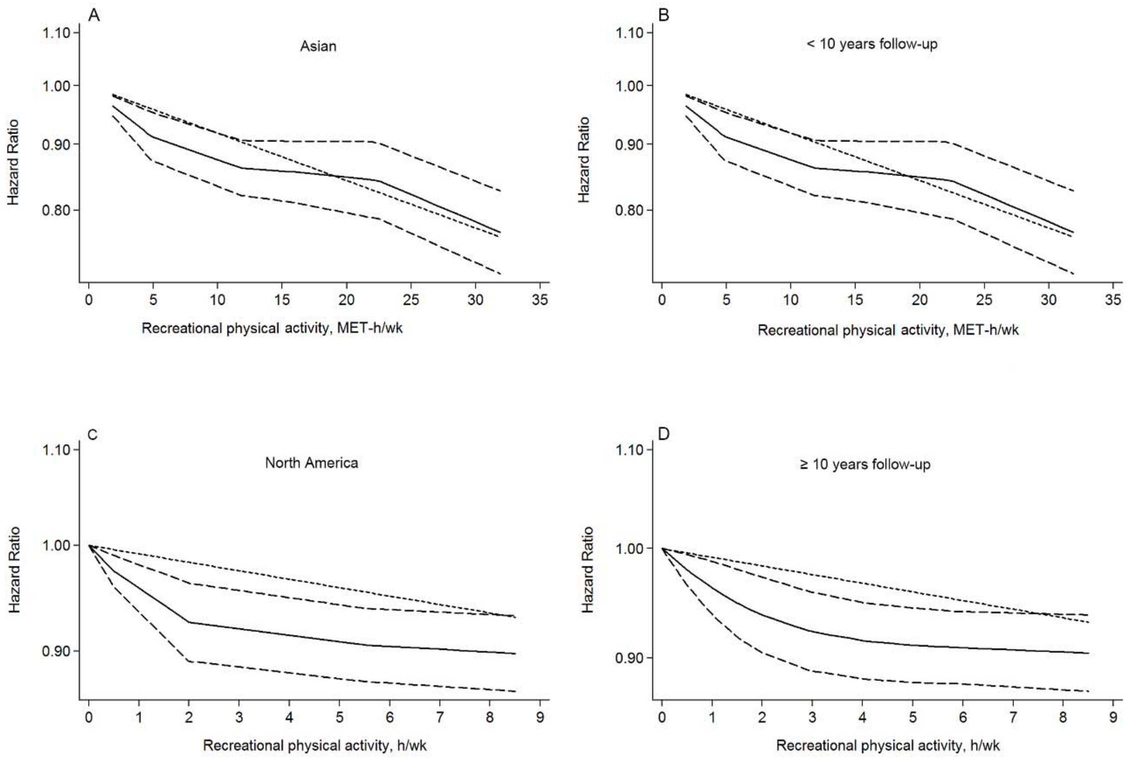
A Sensitivity analysis in the general population studies



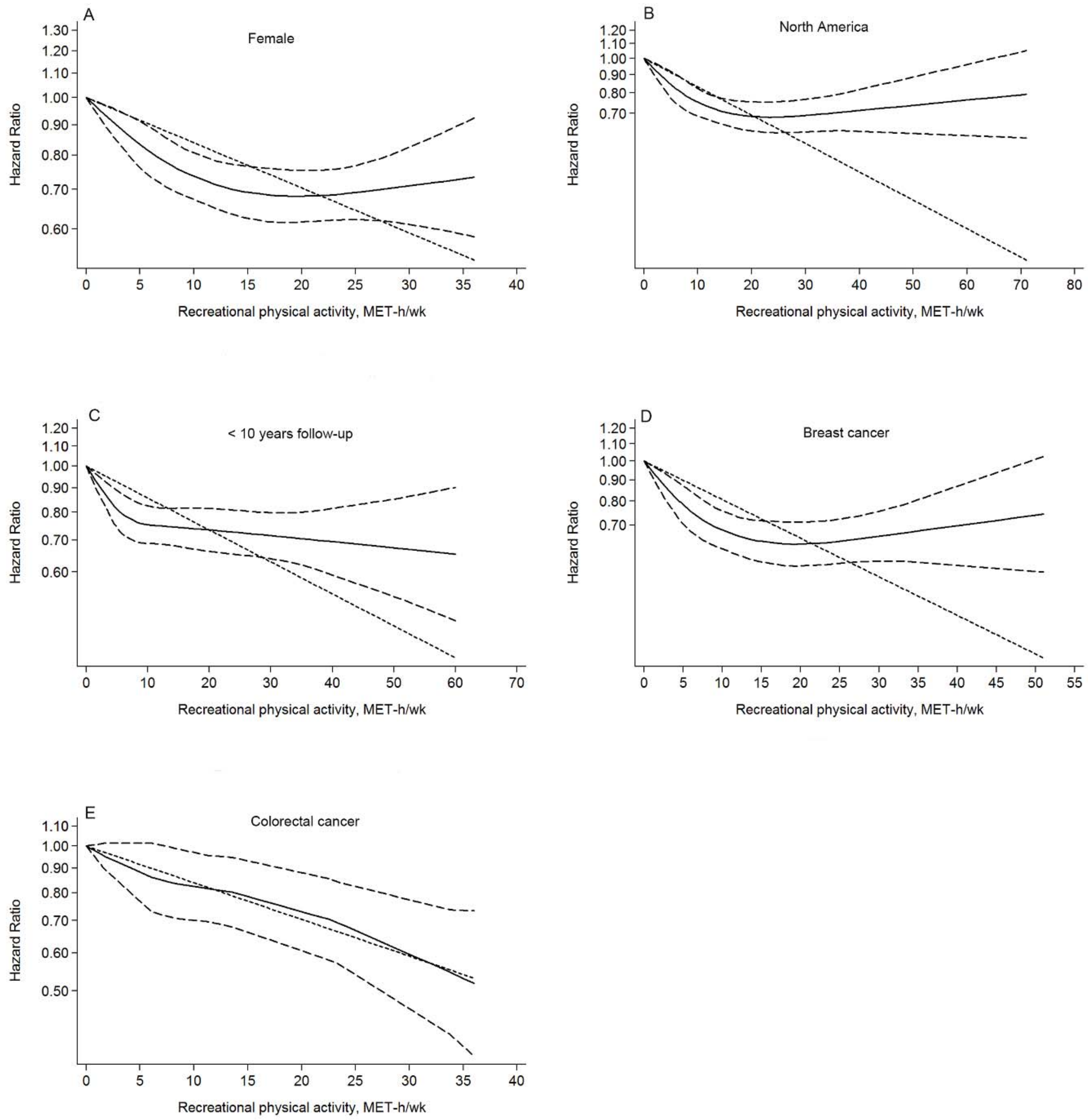
B Sensitivity analysis in cancer survival studies



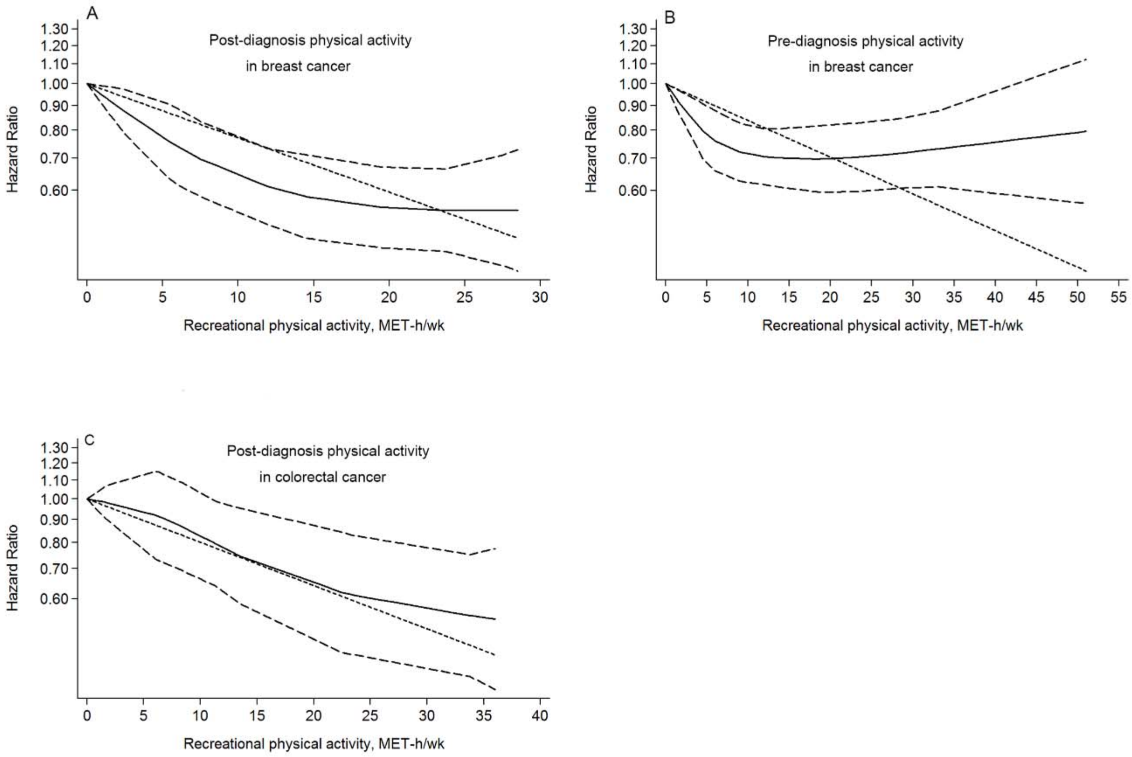
Supplementary figure S3 Dose-response analysis between cancer mortality and recreational physical activity in the general population in the subgroup of Asian (A), < 10 years follow-up (B), North America (C) and ≥ 10 years follow-up (D). The solid line and the long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.



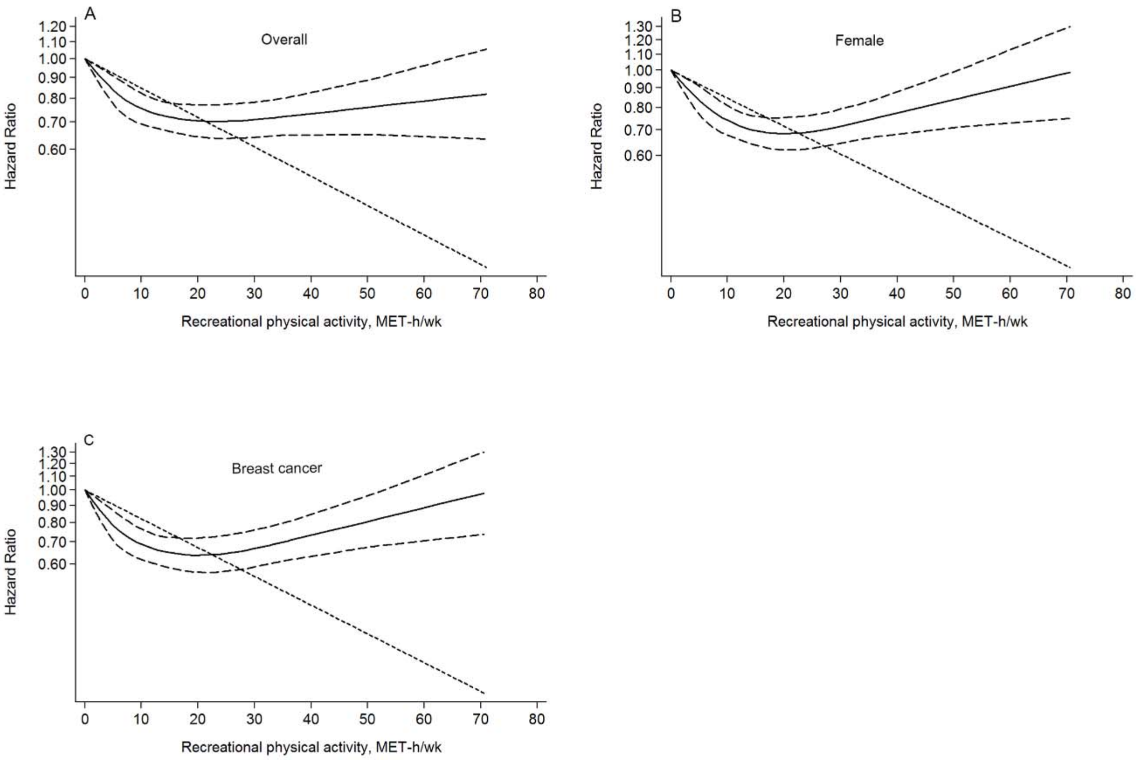
Supplementary figure S4 Dose-response analysis between cancer mortality and recreational physical activity among cancer survivors in the subgroup of female (A), North America (B), ≥ 10 years follow-up (C), breast cancer (D) and colorectal cancer (E). The solid line and the long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.



Supplementary figure S5 Dose-response relation between cancer mortality and recreational physical activity in post-diagnosis and pre-diagnosis. Post-diagnosis physical activity in breast cancer (A), pre-diagnosis physical activity in breast cancer (B), post-diagnosis physical activity in colorectal cancer (C). The solid line and the long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.



Supplementary figure S6 Dose-response relation between recreational physical activity and cancer mortality in models without removing extreme value among cancer survivors. Overall cancer mortality (A), in female (B), in breast cancer (C). The solid line and the long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.



Supplementary table S1 Characteristics of the study included in the meta-analysis on physical activity and cancer mortality

	Author (year) & Country[ref]	Study name	Gender	Age(y) at recruitment	No. death	No. case	No. cohort	Median follow-up(years or person-years)	Cancer type	Type of physical activity	Main results	Adjustment factors
1	Arraiz (1992) Canada [1]	A population-based cohort study	Both	30-69	229		12218	7	All	Total physical activity	Very active: 1.00 Active: 1.40 (0.80-2.30) Moderate: 0.80 (0.40-1.40) Inactive: 1.20 (0.70-1.90)	Age, sex, smoking and alcohol consumption
2	Kampert (1996) USA [2]	A prospective observational study	Both	20-88	223		25341	8	All	Recreational physical activity	(Mean ± SD)s Male Q1(622±151s): 1.00 Q2(817±125s): 0.55 (0.44, 0.7) Q3(950±122s): 0.61 (0.48, 0.78) Q4(1097±133s): 0.52 (0.41, 0.66) Q5(1407±189s): 0.49 (0.37, 0.64) Female Q1(377±109s): 1.00 Q2(536±107s): 0.53 (0.30, 0.95) Q3(628±116s): 0.56 (0.31, 1.01) Q4(763±129s): 0.22 (0.10, 0.49) Q5(1040±215s): 0.37 (0.19, 0.72)	Baseline differences in age, examination year, cigarette smoking, chronic illnesses, and electrocardiogram abnormalities
3	Rosengren (1997) Sweden [3]	The Multifactor Primary Prevention Study	Male	47-55	723		7142	20	All	Recreational physical activity	Sedentary, moderately active, regular exercise, athletic sports. Two most active groups compared to the sedentary group: 0.78 (0.62, 0.99)	Age, serum cholesterol. Smoking, alcohol abuse, and manual versus nonmanual occupational class
4	Smith (2000) UK [4]	The Whitehall Study	Male	40-64	832		6702	25	All	Recreational physical activity	Inactive: 1.28 (1.1, 1.6) Moderately active: 1.13 (0.9, 1.4) Active: 1.00 Active group compared to inactive group with crude HR: 0.65 (0.53, 0.80)	Age, employment grade, BMI, smoking
5	Batty (2001) UK [5]	The Whitehall Study	Male	40-64	1151		18403	25	All	Travel activity Walking or bicycling on the way to work	(Min/day) 0-9: 1.00 10-19: 1.05 (0.90, 1,20) ≥20: 0.99 (0.90, 1.10)	Age, employment grade, BMI, smoking,
6	Kilander (2001) Sweden [6]	A cohort study in Sweden	Male	48.6-51.1	216		2301	25.7	All	Recreational physical activity	Low: 1.09 (0.73, 1.64) Medium: 0.96 (0.70, 1.33) High: 1.00	Age, body height, diastolic blood pressure, systolic blood pressure, b-glucose, BMI, s-triglycerides, s-cholesterol

7	Lee (2002) Korea [7]	The Korea Medical Insurance Corporation (KMIC)	Male	35-64	883	452645	5	Lung cancer	Recreational physical activity	No: 1.00 Yes: 0.80 (0.70, 0.90)	Age
8	Lee (2003) USA [8]	The College Alumni Health Study	Both	47.1 (mean age)	212	32687	5	Pancreatic cancer	Recreational physical activity	(KJ/wk) < 2100: 1.00 2100-4199: 0.98 (0.65, 1.49) 4200-10499: 0.92 (0.62, 1.35) ≥10500: 1.31 (0.69, 1.92)	Age (single years), sex, cigarette smoking, diabetes mellitus
9	Hu (2005) Finland [9]	Prospective follow-up study	Both	25-64	7394	47212	17.7	All	Total physical activity	Male Low: 1.00 Moderate: 0.83 (0.69, 1.00) High: 0.79 (0.65, 0.96) Female Low: 1.00 Moderate: 0.85 (0.71, 1.01) High: 0.73 (0.60, 0.88)	Age, study year, education, smoking status, systolic blood pressure, cholesterol, BMI
10	Nilson (2006) Norway [10]	The HUNT study	Male	41-100	276	29110	17.5	Prostate cancer	Recreational physical activity	No: 1.00 Low: 0.71 (0.50, 1.02) Medium: 0.81 (0.60, 1.10) High: 0.67 (0.78, 0.94)	Age, BMI, marital status , education, alcohol consumption, smoking status
11	Schnohr (2006) Denmark [11]	The Copenhagen City Heart Study	Both	20-93	632	4894	20	All	Recreational physical activity	(h/wk) <2: 1.00 2-4: 0.77 (0.61-0.97) >4: 0.73 (0.56-0.95)	Age, sex, smoking, total-cholesterol, high-density, lipoprotein-cholesterol, systolic blood pressure/antihypertensive drugs, diabetes, alcohol consumption, body mass index, education, income and forced respiratory, volume in the first second of expiration (FEV1), measured at the second examination
12	Huxley (2007) Asia-Pacific region [12]	The Asia Pacific Cohort Studies Collaboration (APCSC)	Both	47	751	539201	6.8	Colorectal cancer	Total physical activity	No: 1.00 Yes: 0.77 (0.60, 0.98)	Smoking, diabetes, and alcohol
13	Lin (2007) Japan [13]	The Japanese Collaborative Cohort study for Evaluation	Both	40-79	402	110792	13	Pancreatic cancer	Recreational physical activity	Walking (min/day) Male <30: 1.00 30: 0.84 (0.46, 1.50)	Age, BMI, cigarette smoking

		of Cancer Risk (JACC)								31-59: 0.68 (0.37, 1.24) ≥60: 0.85 (0.51, 1.41) Female <30: 1.00 30: 1.17 (0.62, 2.22) 31-59: 0.77 (0.40, 1.50) ≥60: 1.04 (0.59, 1.84) Sports (h/wk) Male <1: 1.00 1-2: 0.74 (0.46, 1.19) 3-4: 0.82 (0.45, 1.49) ≥5: 1.04 (0.63, 1.72) Female <1: 1.00 1-2: 0.72 (0.42, 1.22) 3-4: 0.76 (0.37, 1.55) ≥5: 0.88 (0.44, 1.74)	
14	Matthews (2007) China [14]	Shanghai Women's Health Study	Female	40-70	537	67143	5.7	All	Recreational physical activity	(MET-h/wk) ≤9.9: 1.00 10.0-13.6: 1.03 (0.81, 1.32) 13.7-18.0: 0.84 (0.65, 1.08) ≥18.1: 0.77 (0.61, 1.00)	Age, marital status, education, household income, smoking, alcohol drinking, number of pregnancies, oral contraceptive use, menopausal status, other types of physical activity, hypertension, respiratory disease, and chronic hepatitis
15	Orsini (2008) Sweden [15]	The Cohort of Swedish Men (COSM)	Male	45-79	901	37663	9.7	All	Total physical activity	(MET-h/wk) BMI<25 Low (<39): 1.00 Medium(39-44):2.11(1.04, 4.27) High (>44): 2.48 (1.20, 5.12) BMI>25 Low (<39): 1.83 (0.84, 3.99) Medium(39-44):1.90(0.92, 3.94) High (>44): 2.02 (0.98, 4.17)	Age, alcohol consumption, educational level, and parental history with respect to coronary heart disease and cancer
16	Van Dam (2008) USA [16]	The nurses' health study	Female	34-59	4527	77782	24	All	Total physical activity	(h/wk) 0-0.4: 1.00 0.5-1.9: 0.88 (0.79-0.97) 2.0-3.4: 0.83 (0.75-0.93) 3.5-5.4: 0.82 (0.72-0.94) ≥5.5: 0.73 (0.64-0.84)	Age, time period, cigarette smoking, alcohol consumption(g/day), healthy diet score, BMI

17	Orsini (2009) Sweden [17]	A population-based cohort of Swedish men	Male	45-79	199	45887	9	Prostate cancer	Total physical activity	(MET-h/wk) 37(<39): 1.00 41(39-42.2): 0.96 (0.53-1.75) 44(42.5-46): 1.02 (0.55-1.87) 48(>46): 0.98 (0.53-1.83)	Age, waist – hip ratio, height, diabetes, alcohol consumption, smoking status, years of education, total energy intake, consumption of dairy product and red meat and parental history with respect to prostate cancer.
18	Stevens (2009) UK [18]	Million Women Study	Female	55.9±4.5	1710	1300000	8.9	Pancreatic cancer	Recreational physical activity	(Time/wk) <1: 1.0 1: 0.87 2-3: 1.03 ≥4: 1.01	Age, region, socioeconomic status, smoking, BMI and height
19	Autenrieth (2011) Germany [19]	The second MONICA/KORA Augsburg survey	Both	25-74	326	4672	17.8	All	Recreational physical activity	(MET-h/wk) 0: 1.00 <3: 0.58 (0.42-0.80) 3-6: 0.56 (0.40-0.77) >6: 0.36 (0.23-0.59)	Sex, BMI, systolic blood pressure, total-to-HDL cholesterol ratio, education, smoking status, alcohol consumption, myocardial infarction, stroke, diabetes, cancer, self-reported limited physical activity due to health problems, and other domains of physical activity
20	Batty (2011) UK [20]	The Whitehall study	Male	40-69	578	17934	40	Prostate cancer	Recreational physical activity	Recreational physical activity Low: 1.00 Middle: 1.24 (0.88-1.73) High: 1.12(0.76-1.64) Travel activity (Min/day) 0-9: 1.00 10-19: 1.24 (0.88-1.73) 20-29: 1.26 (0.92-1.72) 30-39: 1.3 (0.86-1.97) ≥40: 1.65 (0.87-3.15)	Age at risk, BMI, plasma cholesterol, socio-economic status, diabetes/blood glucose,marital status, FEV1, height, smoking, and diastolic and systolic blood pressure
21	Borch (2011) Norway [21]	The Norwegian Women and Cancer (NOWAC) Study	Female	30-70	1584	66136	12	All	Recreational physical activity	Ten levels 1: 1.32 (0.96-1.81) 2: 1.48 (1.19-1.84) 3: 1.26 (1.06-1.5) 4: 1.07 (0.91-1.25) 5: 1.00 6: 0.88 (0.75-1.03) 7: 0.90 (0.76-1.07) 8: 0.92 (0.74-1.13)	BMI，height, smoking status, years of smoking, amount of smoking, alcohol intake, menopausal status, age at first birth, parity, hormone therapy use, cardiovascular disease diabetes mellitus and

										9: 0.84 (0.60-1.170 10: 0.75 (0.49-1.15)	prevalent cancer
22	Laukkanen (2011) Finland [22]	An eastern Finnish follow-up study	Male	42.0-61.3	181	2560	16.7	All	Recreational physical activity	(MET-h/wk) <3.7: 1.00 3.7-4.4: 0.99 (0.68-1.46) 4.5-5.2: 0.95 (0.64-1.41) >5.2: 0.64 (0.40-1.00)	Age, examination year, cigarette smoking, alcohol consumption, BMI, caloric, fiber and fat intake.
23	McCullough (2011) USA [23]	The Cancer Prevention Study-II Nutrition Cohort (The CPS-II Nutrition Cohort)	Both	50-74	5874	111966	14	All	Recreational physical activity	(MET-h/wk) Male <8.75: 1.00 8.75-17.5: 1.00 (0.91-1.09) >17.5: 1.00 (0.92-1.08) Female <8.75: 1.00 8.75-17.5: 0.97 (0.88-1.08) >17.5: 0.99 (0.89-1.09)	Age, smoking status, education, BMI, alcohol intake, health diet score
24	Morrison (2011) England [24]	The Whitehall I study	Male	40-69	329	17949	40	Colorectal cancer	Recreational physical activity	(Min/day) Colon cancer 0-9: 1.00 10-19: 1.09 (0.92-1.28) ≥20: 0.88 (0.61-1.26) Rectal cancer 0-9: 1.00 10-19: 0.91 (0.71-1.16) ≥20: 0.74 (0.43-1.26)	Age, height, BMI, plasma cholesterol, diabetes, socioeconomic, smoking
25	Nakamura (2011) Japan [25]	A population-based prospective study	Both	54.7±12.4 (Male) 55.8±13.2 (Female0	51	30826	212247 (person-years)	Pancreatic cancer	Recreational physical activity	Male Low: 1.00 Middle: 1.13 (0.48-2.67) High: 1.03 (0.41-2.60) Female Low: 1.00 Middle: 1.56 (0.44-5.56) High: 3.29 (0.96-11.2)	Age, smoking status, BMI, history of diabetes mellitus
26	Wen (2011) China [26]	A historically prospective cohort study	Both	≥20	4722	11802	8.05	All	Recreational physical activity	(MET-h/wk) Overall <3.75: 1.00 3.75-7.49: 0.90 (0.83-0.99) 7.50-16.49: 0.85 (0.77-0.93) 16.50-25.49: 0.85 (0.75-0.97) ≥25.5: 0.78 (0.69-0.88) Colorectal cancer <3.75: 1.00 3.75-7.49: 1.08 (0.83-1.41) 7.50-16.49: 0.71 (0.52-0.96) 16.50-25.49: 0.84 (0.56-1.25) ≥25.5: 0.77 (0.53-1.12)	Age, sex, education, activity at work, smoking, drinking, fasting blood glucose, systolic blood pressure, body mass index, diabetes history, and hypertension history

										Liver cancer <3.75: 1.00 3.75-7.49: 0.97 (0.80-1.41) 7.50-16.49: 0.92 (0.75-1.12) 16.50-25.49: 0.80 (0.60-1.07) ≥25.5: 0.65 (0.49-0.86) Breast cancer <3.75: 1.00 3.75-7.49: 0.99 (0.64-1.52) 7.50-16.49: 1.40 (0.89-2.21) 16.50-25.49: 1.73 (0.96-3.11) ≥25.5: 0.86 (0.37-2.01) Lung cancer <3.75: 1.00 3.75-7.49: 0.73 (0.59-0.90) 7.50-16.49: 0.93 (0.77-1.14) 16.50-25.49: 0.78 (0.59-1.04) ≥25.5: 0.79 (0.61-1.02)	
27	Mok (2012) Korea [27]	A cohort study in Korea	Both	30-93	1060	59636	10.3	Colorectal cancer	Recreational physical activity	(MET-min/wk) Male 0: 1.00 3.5-10000: 0.66 (0.53-0.81) >1000: 0.79 (0.64-0.96) Female 0: 1.00 3.5-1000: 0.62 (0.41-0.92) >1000: 0.66 (0.42-1.06)	Age, smoking status, alcohol intake, body mass index, hypertension, total cholesterol, and diabetes
28	Parekh (2012) USA [28]	The NHANES III (Third National Health and Nutrition Examination Survey)	Both	20-89	860	15535	18	All	Recreational physical activity	(MET-min/wk) <1.16: 1.00 1.16-10.47: 0.85 (0.67-1.08) 10.48-32: 0.74 (0.56-0.98) >48.33: 0.89 (0.68-1.16)	Age, race, sex, and smoking
29	Sahlqvist (2013) England [29]	EPIC-Norfolk cohort	Both	40-79	700	13346	11.5	All	Recreational physical activity	(Min/wk) 0: 1.00 1-59: 0.95 (0.71-1.25) ≥60: 1.12 (0.80-1.58)	Age, sex, education level, social class, smoking status, family history of cancer or cardiovascular disease, all other physical activity
30	Vergnaud (2013) Europe [30]	The European Prospective Investigation into Cancer and Nutrition	Both	25-70	9388	378864	12.8	All	Total physical activity	HR of cancer death per 1-unit increase of each World Cancer Research Fund (WCRF)/ (>0.5 points) AICR score component: 0.90 (0.86-0.94)	sex, age at recruitment, and center and adjusted for educational level, smoking status and intensity of smoking, and

		study (EPIC)									menopause status and all WCRF/AICR components were mutually adjusted.
31	Wang (2013) China [31]	The Shanghai Men's Health Study (SMHS)	Male	40-74	1053	61477	5.48	All	Total physical activity	(MET-h/wk) No regular exercise: 1.00 <13.9: 0.81 (0.68-0.96) ≥13.9: 0.81 (0.86-0.94)	Age, educational level, income, occupation, alcohol consumption, pack-years of smoking, daily intake of energy, red meat, fruits, and vegetables, daily physical activity other than exercise, body mass index, and history of cardiovascular disease, diabetes, hypertension, chronic liver disease, or pulmonary disease
32	Williams (2013) USA [32]	The National Walkers' and Runners' Health Studies	Female	/	101	79124	11.0	Breast cancer	Running and Walking	(MET-h/wk) <13.9: 1.00 7.5-12.5: 0.47 (0.21-0.97) ≥12.5: 0.61 (0.38-1.01)	Follow-up age, race, menopause, oral contraceptive and estrogen/progesterone use, BMI
33	Yu (2013) China [33]	A cohort study on osteoporosis and general health in Hong Kong	Both	≥65	452	2867	9.2	All	Recreational physical activity	Male Light Inactive: 1.00 Active: 1.01 (0.70-1.46) Moderate Inactive: 1.00 Active: 1.18 (0.79-1.77) Strenous/muscle-conditioning Inactive: 1.00 Active: 0.89 (0.57-1.39) Female Light Inactive: 1.00 Active: 0.70 (0.41-1.21) Moderate Inactive: 1.00 Active: 0.38 (0.14-1.07) Strenous/muscle-conditioning Inactive: 1.00 Active: 0.93 (0.29-2.95)	Age, education level, Hong Kong ladder, total energy intake, DQI, smoking, and alcohol use, BMI, frailty index, living arrangement, and level of leisure time physical activity/housework
34	Arem (2014) USA [34]	The NIH–AARP	Both	50-71	15001	293511	12.1	All	Recreational physical activity	(h/wk) All cancers	Sex, BMI, education, race, alcohol, healthy

Diet and Health Study		Never: 1.00 <1: 0.95 (0.89-1.01) 1-3: 0.93 (0.88-0.98) 4-7: 0.90 (0.85-0.95) >7: 0.89 (0.84-0.94) Lymphocytic leukemia Never: 1.00 <1: 0.96 (0.48-1.89) 1-3: 1.3 (0.76-2.21) 4-7: 0.65 (0.35-1.19) >7: 0.68 (0.37-1.25) Colon Never: 1.00 <1: 0.80 (0.63-1.01) 1-3: 0.85 (0.70-1.02) 4-7: 0.79 (0.65-0.96) >7: 0.70 (0.57-0.85) Liver Never: 1.00 <1: 0.79 (0.54-1.14) 1-3: 0.90 (0.68-1.21) 4-7: 0.64 (0.47-0.88) >7: 0.71 (0.52-0.98) Oral cavity and pharynx Never: 1.00 <1: 0.83 (0.48-1.44) 1-3: 0.79 (0.51-1.24) 4-7: 0.76 (0.48-1.21) >7: 0.75 (0.47-1.20) Non-Hodgkins lymphoma Never: 1.00 <1: 1.19 (0.90-1.58) 1-3: 0.76 (0.58-0.98) 4-7: 0.83 (0.64-1.06) >7: 0.80 (0.62-1.04) Esophagus Never: 1.00 <1: 0.92 (0.65-1.29) 1-3: 0.91 (0.69-1.20) 4-7: 0.96 (0.73-1.27) >7: 0.80 (0.60-1.08) Myeloma Never: 1.00 <1: 0.75 (0.49-1.14) 1-3: 0.56 (0.40-0.81) 4-7: 0.77 (0.55-1.07)	eating index 2010 score, calories, marriage status, diabetes and smoke level

>7: 0,84 (0.77-0.92)
Lung
Never: 1.00
<1: 0.85 (0.76-0.95)
1-3: 0.92 (0.84-1.00)
4-7: 0.82 (0.75-0.90)
>7: 0.84 (0.77-0.92)
Myeloid/monocytic
Never: 1.00
<1: 1.27 (0.86-1.86)
1-3: 0.85 (0.60-1.21)
4-7: 1.10 (0.79-1.54)
>7: 0.86 (0.60-1.22)
Stomach
Never: 1.00
<1: 1.00 (0.65-1.56)
1-3: 0.99 (0.69-1.42)
4-7: 0.97 (0.67-1.40)
>7: 0.90 (0.61-1.31)
Ovarian
Never: 1.00
<1: 0.92 (0.62-1.36)
1-3: 0.83 (0.59-1.150
4-7: 0.87 (0.63-1.21)
>7: 0.91 (0.65-1.31)
Prostate
Never: 1.00
<1: 0.97 (0.69-1.37)
1-3: 0.79 (0.59-1.06)
4-7: 1.03 (0.78-1.37)
>7: 0.93 (0.69-1.240
Bladder
Never: 1.00
<1: 1.25 (0.84-1.86)
1-3: 0.97 (0.68-1.38)
4-7: 0.95 (0.67-1.36)
>7: 1.03 (0.72-1.46)
Breast
Never: 1.00
<1: 1.21 (0.82-1.80)
1-3: 0.92 (0.65-1.29)
4-7: 0.97 (0.68-1.37)
>7: 1.08 (0.76-1.53)
Brain
Never: 1.00
<1: 1.14 (0.78-1.66)

										1-3: 1.03 (0.75-1.42) 4-7: 0.91 (0.65-1.26) >7: 1.14 (0.82-1.56) Endometrial Never: 1.00 <1: 1.52 (0.85-2.69) 1-3: 0.79 (0.45-1.38) 4-7: 1.13 (0.66-1.93) >7: 1.21 (0.70-2.08) Pancreas Never: 1.00 <1: 1.35 (1.07-1.70) 1-3: 1.14 (0.80-1.64) 4-7: 1.28 (1.05-1.56) >7: 1.25 (1.03-1.53) Kidney Never: 1.00 <1: 1.10 (0.71-1.70) 1-3: 1.14 (0.80-1.64) 4-7: 1.47 (1.03-2.09) >7: 1.42 (0.98-2.03) Rectum Never: 1.00 <1: 1.26 (0.64-2.48) 1-3: 1.57 (0.90-2.71) 4-7: 1.27 (0.72-2.25) >7: 1.63 (0.93-2.84)	
35	Hastert (2014) USA [35]	Vitamins and Lifestyle (VITAL) cohort	Both	50-76	1595	57841	7.7	All	Recreational physical activity	<30 min/day or <5 day/wk or <7 of the previous 10 years of moderate or fast walking and/or moderate or strenuous activity: 1.00 >30 minutes/day of moderate or fast walking and/or moderate or trenuous activity on at least 5 days/wk in at least 7 of the past 10 years: 0.91 (0.79-1.04)	Age, sex, education, race/ethnicity, marital status, PSA screening in previous 2 years, colonoscopy or sigmoidoscopy in previous 10 years, cancers diagnosed in first-degree relatives, non-steroidal anti-inflammatory medication and regular or low-dose aspirin use, pack-years of smoking, and kilocalories of average daily energy intake. Several additional reproductive factors were included for women, including age at

												menarche, age at birth of first child, years of estrogen-only, and of combined estrogen plus progestin hormone therapy use,hysterectomy, and age at menopause
36	Wanner (2014) Switzerland [36]	The National Research Program 1A and Swiss MONICA study	Both	16-92	1351		17663	20.2	All	Recreational physical activity	Female and Male Low: 1.00 Moderate: 0.92 (0.82-1.04) High: 0.69 (0.54-0.90) Male Low: 1.00 Moderate: 0.91 (0.77-1.06) High: 0.63 (0.47-0.86) Female Low: 1.00 Moderate:0.91 (0.76-1.09) High: 1.04 (0.66-1.660	Age, educational level, marital status, survey, smoking and nutrition
37	Rohan (1995) Austrialia [37]	A population-based cohort of breast cancer patients	Female	20-74	112	411		5.5	Breast cancer	Recreational physical activity	(Kcal/wk) 0: 1.00 0-2000: 1.42 (0.78-2.60) 2000-4000: 0.73 (0.37-1.42) >4000: 0.98 (0.50-1.94)r	Age, ER and PR status, tumour diameter, years of education, history of benign breast, disease, age at menarche, age at first live birth, height, Quetelet's index, energy intake and menopausal status
38	Enger (2004) USA [38]	A population-based case–control study	Female	21-40	251	717		10.4	Breast cancer	Recreational physical activity	(h/wk) 0: 1.00 0.1-3.7: 0.86 (0.61-1.21) >3.8: 1.34 (0.72-2.47)	Age, stage at diagnosis and BMI
39	Borugian (2004) Canada [39]	A cohort study from the Vancouver Cancer Centre (VCC) of the British Columbia Cancer Agency	Female	19-75	112	603		10	Breast cancer	Total physical activity	Pre-diagnosis Climbing (Flight) None: 1.00 1-4: 1.20 (0.70-2.20) 5-8: 1.40 (0.80-2.60) >9: 1.10 (0.50-2.20) Walking (Block) None: 1.00 1-4: 1.10 (0.60-1.90) 5-8: 1.00 (0.50-1.90) >9: 1.00 (0.50-1.90) Sports	Total caloric intake, age, stage at diagnosis

										None: 1.00 A few time/year: 1.10(0.60-2.00) A few time/month:1.20(0.40-2.60) 1 time/wk: 0.70 (0.30-1.70) >1 time/wk: 1.00 (0.50-1.90) Exercise None: 1.00 A few time/year: 1.10 (0.60-2.00) A few time/month: 1.20 (0.40-2.60) 1 time/wk: 0.70 (0.30-1.70) >1 time/wk: 1.00 (0.50-3.20) Jogging None: 1.00 A few time/year: 1.50 (0.50-4.10) A few time/month: 1.90 (0.70-5.40) 1 time/wk: 1.80 (0.40-7.50) >1 time/wk: 1.80 (0.40-7.50) Swimming None: 1.00 A few time/year: 1.20 (0.60-2.400 A few time/month: 1.00 (0.50-2.00) 1 time/wk: 1.20 (0.70-2.30) >1 time/wk: 0.90 (0.50-1.50) Gardening None: 1.00 A few time/year: 1.00 (0.60-1.80) A few time/month: 1.60 (0.90-2.70) 1 time/wk: 1.00 (0.60-1.70) >1 time/wk: 0.80 (0.50-1.40)	
40	Holmes (2005) USA [40]	The Nurses' Health Study (NHS) cohort	Female	30-55	463	2987	8.0	Breast cancer	Recreational physical activity	(MET-h/wk) Post-diagnosis <3: 1.00 3-8.9: 0.80 (0.60-1.06) 9-14.9: 0.50 (0.31-0.82) 15-23.9: 0.56 (0.38-0.84) ≥24: 0.60 (0.40-0.89) Pre-diagnosis (BMI<25) <3: 1.00 3-8.9: 0.65 (0.43-0.97) 9-14.9: 0.35 (0.18-0.68) 15-23.9: 0.63 (0.39-1.04) ≥24: 0.61 (0.37-0.99) Pre-diagnosis (BMI≥25) <3: 1.00 3-8.9: 1.01 (0.66-1.55) 9-14.9: 0.81 (0.38-1.72)	Age, interval between diagnosis and physical activity assessment, body mass index, menopausal status and hormone therapy use, age at first birth and parity, oral contraceptive use, disease stage, radiation treatment, chemotherapy, and tamoxifen treatment,

										15-23.9: 0.44 (0.21-0.93) ≥24: 0.52 (0.26-1.06)	
41	Abrahamson (2006) USA [41]	A follow-up study	Female	20-54	212	1264	8.5	Breast cancer	Recreational physical activity	(MET-h/wk) Pre-diagnosis 1.6-16.6: 1.00 16.7-29.4: 0.74 (0.50-1.11) 29.5-43.0: 0.97 (0.66-1.41) 43.1-98.0: 1.12 (0.78-1.62)	Stage and income
42	Haydon (2006) Austrialia [42]	The Melbourne Collaborative Cohort Study (MCCS)	Both	25-75	181	526	5.5	Colorectal cancer	Recreational physical activity	Pre-diagnosis No exercise: 1.00 Exercise: 0.73 (0.54-1.00)	Age, sex, stage
43	Meyerhardt (2006) USA [43]	The Nurses' Health Study (NHS) cohort	Female	20-54	72	554	9.6	Colorectal cancer	Recreational physical activity	(MET-h/wk) Post-diagnosis <3: 1.00 3-8.9: 0.92 (0.50-1.69) 9-17.9: 0.57 (0.27-1.20) ≥18: 0.39 (0.18-0.82) Pre-diagnosis <3: 1.00 3-8.9: 0.83 (0.45-1.53) 9-17.9: 1.05 (0.56-1.99) ≥18: 0.86 (0.44-1.67)	BMI，stage of disease, grade of tumor differentiation, colon or rectal primary, age at diagnosis, year of diagnosis, receipt of chemotherapy, time from diagnosis to physical activity measurement, change in body mass index before and after diagnosis, smoking status
44	Holick (2008) USA [44]	Collaborative Women's Longevity Study (CWLS)	Female	20-79	109	4482	5.6	Breast cancer	Recreational physical activity	(MET-h/wk) Post-diagnosis Overall <2.8: 1.00 2.8-7.9: 0.62 (0.37-1.03) 8.0-20.9: 0.53 (0.31-0.88) ≥21.0: 0.44 (0.25-0.76) Moderate <2.0: 1.00 2.0-3.9: 0.69 (0.43-1.12) 4.0-10.2: 0.47 (0.27-0.83) ≥10.3: 0.41 (0.24-0.73) Vigorous 0: 1.00 0.1-5.9: 0.94 (0.55-1.61) 6.0-15.0: 1.07 (0.65-1.76) ≥15.1: 0.90 (0.47-1.72)	Age at diagnosis, stage of disease at diagnosis, state of residence at diagnosis, and interval between diagnosis and physical activity assessment
45	Sundelof (2008) Sweden [45]	Swedish Oesophageal and Cardia Cancer study	Both	/	510	580	10	Oesophageal adenocarcinoma, Oesophageal	Recreational physical activity	Pre-diagnosis Oesophageal adenocarcinoma 1st (low): 1.00 2nd: 0.90 (0.50-1.50)	Age, sex, education, symptomatic gastroesophageal reflux, BMI, tobacco smoking,

		(SECC study)						squamous-cell carcinoma, Gastric cardia adenocaricnoma		3rd: 0.70 (0.40-1.20) 4th (high): 0.90 (0.50-1.50) Oesophageal squamous-cell carcinoma 1st (low): 1.00 2nd: 1.00 (0.60-1.70) 3rd: 0.90 (0.50-1.60) 4th (high): 0.80 (0.40-1.50) Gastric cardia adenocaricnoma 1st (low): 1.00 2nd: 0.90 (0.60-1.40) 3rd: 1.00 (0.70-1.50) 4th (high): 0.80 (0.50-1.20)	alcohol intake, tumour stage and oesophagectomy
46	Yang (2008) Sweden [46]	A prospective follow-up study	Female	50-74	396	635	8.0	Ovarian cancer	Recreational physical activity	(h/wk) Pre-diagnosis None: 1.00 <1: 1.23 (0.87-1.75) 1-2: 1.15 (0.85-1.57) >2: 1.18 (0.87-1.61)	Age at diagnosis, epithelial ovarian cancer FIGO stage and WHO grade of differentiation
47	Dal Maso (2008) Italy [47]	A follow-up study carried out in 6 Italian areas	Female	23-47	398	1453	12.6	Breast cancer	Recreational physical activity	(h/wk) Pre-diagnosis <2: 1.00 ≥2: 0.85 (0.68-1.07)	Region of residence, age at diagnosis, year of diagnosis, TNM stage and ER/PR status
48	Duffy (2009) USA [48]	A prospective cohort study	Both	>18	166	504	2.74	Head and Neck Squamous Cell Carcinoma	Total physical activity	PASE physical activity score (per 10 points): 0.98 (0.95-1.00)	Age, marital status, education, smoking status, alcohol problem, fruit intake, BMI
49	Meyerhardt (2009) USA [49]	The Health Professional Follow-up Study (HPFS) cohort	Male	/	88	668	7.8	Colorectal cancer	Recreational physical activity	(MET-h/wk) Post-diagnosis 0.0-3.0: 1.00 3.1-9.0: 1.06 (0.55-2.08) 9.1-18.0: 1.30 (0.65-2.59) 18.1-27.0: 0.76 (0.33-1.77) >27: 0.47 (0.24-0.92)	Age at diagnosis, stage of disease, grade of tumor differentiation, colon or rectal primary, year of diagnosis, body mass index at diagnosis, time from diagnosis to physical activity measurement, change in body mass index prior and after diagnosis, smoking status
50	Sternfeld (2009) USA [50]	The life after Cancer Epidemiology (LACE) study	Female	18-79	102	1868	7.25	Breast cancer	Total physical activity	Post-diagnosis Total (MET-h/wk) <29: 1.00 29-44: 1.01 (0.57-1.78) 44-62: 0.70 (0.38-1.29) >62: 0.87 (0.48-1.59)	Age, stage, weigh at 18y, type of treatment, type of surgery

										Moderate-vigorous <5.3: 1.00 5.3-15: 0.77 (0.44-1.34) 15-27: 0.47 (0.24-0.91) >27: 0.90 (0.51-1.58) Moderate (h/wk) <1: 1.00 1-3: 0.65 (0.36-1.26) 3-6: 0.69 (0.40-1.19) >6: 0.73 (0.40-1.33) Vigorous (h/wk) 0: 1.00 0-1: 0.79 (0.42-1.48) >1: 1.10 (0.68-1.80)	
51	West-Wright (2009) USA [51]	The California Teachers Study	Female	18-54	221	3539	9	Breast cancer	Recreational physical activity	Pre-diagnosis ≤0.5 h/wk/y of any activity: 1.00 0.51-3.0 h/wk/y of moderate or strenuous activity: 0.65 (0.45-0.93) >3.0 h/wk/y either activity type: 0.53 (0.35-0.80)	Race, BMI, total caloric intake, number of comorbid conditions, and estrogen receptor status
52	Friedenreich (2009) Canada [52]	A prospective cohort study	Female	/	223	1231	10.3	Breast cancer	Recreational physical activity	(MET-h/wk) Recreational ≤5: 1.00 5-10: 0.68 (0.47-0.98) 10-19: 0.65 (0.45-0.94) >19: 0.54 (0.36-0.79) Total ≤95: 1.00 95-120: 0.70 (047-1.04) 120-150: 0.81 (0.56-1.18) >151: 0.79 (0.53-1.17) Household ≤5: 1.00 5-10: 0.70 (0.47-1.04) 10-19: 0.81 (0.56-1.18) >19: 0.79 (0.53-1.17) Moderate 0-1.4: 1.00 1.4-3.9: 0.67 (0.50-0.91) ≥3.9: 0.56 (0.38-0.82) Vigorous <0.03: 1.00 ≥0.03: 0.74 (0.56-0.98)	Age, tumor stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, BMI and other comorbidity conditions
53	Hellmann (2010) Denmark [53]	Copenhagen City Heart Study(CCHS)	Female	/	323	528	7.8	Breast cancer	Recreational physical activity	Pre-diagnosis (h/wk) Inactive <2: 1.00	Alcohol, smoking, physical activity, body mass index, hormone

										Moderate 2-4: 0.83 (0.55-1.87) High >4: 1.01 (0.62-1.63)	replacement therapy, age, disease stage, menopausal status, parity, education, and adjuvant treatment
54	Keegan (2010) USA [54]	A population-based follow-up study	Female	18-69	605	3833	7.8	Breast cancer	Recreational physical activity	Pre-diagnosis (MET-h/wk) ≤6.7: 1.00 6.8-16.3: 0.86 (0.67-1.11) 16.4-26.1: 0.84 (0.64-1.10) 26.2-46.0: 0.88 (0.68-1.14) >46.0: 0.93 (0.72-1.21)	Study center, age of diagnosis, race/ethnicity, number of affected nodes, BMI, time since last full term pregnancy, ER status, PR status, tumor grade, tumor size, and tumor type
55	Emaus (2010) Norway [55]	Norwegian Counties Study	Female	27-79	355	1364	8.2	Breast cancer	Recreational physical activity	Pre-diagnosis Sedentary: 1.00 Moderate: 0.92 (0.71-1.19) Hard: 0.75 (0.49-1.15)	Age at diagnosis, pre-diagnostic observation time, tumor stage, region of residence (strata), year at diagnosis before and after 1995 (strata), and BMI
56	Baade (2011) Austrialia [56]	A longitudinal study	Both	21-82	345	1825	4.9	Colorectal cancer	Recreational physical activity	Post-diagnosis (Min/wk) 0: 1.00 1-149: 0.90 (0.69-1.17) ≥150: 0.88 (0.68-1.15)	Sex, age, BMI, smoking status, marital status, education level，private health insurance, site，stage of disease, treatment, comorbidities
57	Irwin (2011) USA [57]	The Women's Health Initiative (WHI)	Female	50-79	194	4646	6	Breast cancer	Recreational physical activity	(MET-h/wk) Pre-diagnosis Moderate-vigorous 0: 1.00 0.1-3.0: 0.83 (0.51-1.37) 3.1-8.9: 0.82 (0.55-1.22) ≥9: 0.71 (0.49-1.03) Moderate 0: 1.00 0.1-3.00.91 (0.58-1.41): 3.1-8.9: 0.87 (0.60-1.25) ≥9: 0.60 (0.40-0.90) Post-diagnosis Moderate-vigorous 0: 1.00 0.1-3.0: 0.30 (0.09-0.99) 3.1-8.9: 0.77 (0.43-1.38) ≥9: 0.61 (0.35-0.99) Moderate 0: 1.00 0.1-3.0: 0.37 (0.15-0.94)	Age, ethnicity, stage, WHI study arm, previous hormone therapy use, BMI, diabetes, alcohol, smoke, total calories, percentage calories from fat, and servings of fruit and vegetables

										3.1-8.9: 0.71 (0.42-1.20) ≥9: 0.51 (0.30-0.87)	
58	Kenfield (2011) USA [58]	The Health Professionals Follow-Up Study	Male	/	112	2705	9.7	Prostate cancer	Recreational physical activity	Post-diagnosis Total (MET-h/wk) <3: 1.00 3-9: 0.91 (0.48-1.73) 9-24: 0.60 (0.32-1.11) 24-48: 0.83 (0.44-1.55) ≥48: 0.42 (0.20-0.88) Vigorous (h/wk) 1: 1.00 1-3: 1.13 (0.70-1.83) ≥3: 0.39 (0.18-0.84)	Age at diagnosis, months since diagnosis, clinical stage, Gleason score, treatment, and post-diagnosis body mass index, pre-diagnosis physical activity
59	Morikawa (2011) USA [59]	The Nurses' Health Study and the Health Professionals Follow-up Study	Both		68	955	11.8	Colorectal cancer	Recreational activity	Post-diagnosis (MET-h/wk) Negative Nuclear CTNNB1 Status <18: 1.00 ≥18: 0.33 (0.13-0.81) Positive Nuclear CTNNB1 Status <18: 1.00 ≥18: 1.07 (0.50-2.30)	The CTNNB1 variable, age, sex, body mass index, tumor location, tumor differentiation, family history of colorectal cancer in any first-degree relative, microsatellite instability, CpG island methylator phenotype, mutations in KRAS, BRAF, or PIK3CA, level of long interspersed nucleotide element 1 methylation, and tumor protein p53
60	Beasley (2012) USA, China [60]	LACE (the Life After Cancer Epidemiology), NHS (Nurses' Health Study), SBCSS(Shanghai Breast Cancer Survival Study), WHEL(Women's Healthy Eating and Living)	Female	/	971	11282		Breast cancer	Recreational physical activity	Post-diagnosis (MET-h/wk) 0-0.2: 1.00 2.3-4.9: 1.00 (0.71-1.06) 8.0-11.9: 0.87 (0.60-0.91) 16.2-21.4: 0.74 (0.59-0.91) 29.7-48.0: 0.73 (0.59-0.91)	Age at diagnosis, race, menopausal status, TNM stage, hormone receptor status, treatment, post-diagnosis body mass index, and smoking status

61	Cleveland (2012) USA [61]	The Long Island Breast Cancer Study Project	Female	/	120	1273	5.56	Breast cancer	Recreational physical activity	Pre-diagnosis (MET-h/wk) Total 0: 1.00 0-9: 0.61 (0.40-0.92) ≥9: 0.66 (0.42-1.06) Moderate 0: 1.00 0-9: 0.60 (0.39-0.91) ≥9: 0.73 (0.44-1.20) Vigorous 0: 1.00 0-9: 1.61 (0.75-1.79) ≥9: 0.83 (0.59-0.91)	Age at diagnosis, body mass index and menopausal status
62	Kuiper (2012) USA [62]	WHI(The Women's Health Initiative)	Female	50-79	171	1339	11.9	Colorectal cancer	Recreational physical activity	(MET-h/wk) Pre-diagnosis 0: 1.00 0-2.9: 0.98 (0.58-1.66) 3.0-8.9: 1.01 (0.65-1.57) 9.0-17.9: 0.74 (0.46-1.20) ≥18.0: 0.68 (0.41-1.13) Post-diagnosis 0: 1.00 0-2.9: 0.49 (0.21-1.14) 3.0-8.9: 0.30 (0.12-0.73) 9.0-17.9: 0.53 (0.22-1.25) ≥18.0: 0.29 (0.11-0.77)	Age at diagnosis, study arm, BMI, tumor stage, ethnicity, education, alcohol, smoking, and hormone therapy use
63	Arem (2013) USA [63]	WHI(The Women's Health Initiative)	Female	50-79	66	983	5.3	Endometrial cancer	Recreational physical activity	Pre-diagnosis (MET-h/wk) 0: 1.00 0-11.26: 0.51 (0.26-1.01) ≥11.26: 1.05 (0.79-1.38)	Age, BMI, tumor grade, tumor stage, and age at menarche, and lag time from baseline measure to endometrial cancer diagnosis
64	Arem (2013) USA [64]	The NIH–AARP Diet and Health Study	Female	50-71	133	1400	13	Endometrial cancer	Recreational physical activity	Pre-diagnosis (h/wk) Moderate-vigorous Never/rarely: 1.00 <1: 1.26 (0.59-2.70) 1-3: 0.45 (0.19-1.04) 4-7: 0.96 (0.46-2.03) >7: 0.91 (0.43-1.93)	Tumor grade, tumor stage, surgery, chemotherapy, race, family history of breast cancer, diabetes, smoking status, and continuous body mass index
65	Campbell (2013) USA [65]	CPS-II	Both	/	379	2293	8.1	Colorectal cancer	Recreational physical activity	(MET-h/wk) Pre-diagnosis <3.5: 1.00	Age at diagnosis, sex, smoking status, body mass index, red meat

										3.5-8.75: 0.68 (0.49-0.95) ≥8.75: 0.78 (0.57-1.08) Post-diagnosis <3.5: 1.00 3.5-8.75: 1.00 (0.64-1.56) ≥8.75: 0.87 (0.61-1.24)	intake, Surveillance, Epidemiology, and End Results (SEER) summary stage at diagnosis, leisure-time spent sitting, and education
66	Jeon (2013) National [66]	GALGB	Female	/	169	237	7.3	Colorectal cancer	Recreational physical activity	Post-diagnosis (MET-h/wk) <3: 1.00 3-17.9: 0.85 (0.58-1.23) ≥18: 0.71 (0.46-1.11)	Sex, age, body mass index (BMI), depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, and treatment group
67	Schmidt (2013) Germany [67]	MARIE study	Female	50-74	367	3393	5.6	Breast cancer	Recreational physical activity	Pre-diagnosis (MET-h/week) None: 1.00 <12: 0.74 (0.51-1.08) 12-24: 0.82 (0.55-1.22) 24-42: 0.97 (0.65-1.44) ≥42: 0.80 (0.53-1.21)	Tumor size, nodal status, tumor grading, ER/PR status, radiotherapy, screening-detected tumor, HT use at diagnosis, age at diagnosis, BMI pre-diagnosis, smoking status and pack years and pre-existing angina pectoris. In addition, models for overall mortality and for other deaths were adjusted for pre-existing hypertension, previous stroke and use of insulin
68	Tao (2013) USA [68]	WEB study	Female	35-79	170	1170	7.28	Breast cancer	Total physical activity	Pre-diagnosis (h/wk) <3: 1.00 3-6: 0.64 (0.36-1.13) >6: 0.62 (0.34-1.11)	Age at diagnosis, education, BMI, menopausalstatus, TNM, radiotherapy, chemotherapy, hormonal therapy, p53 mutation, HER2 status,ER status, and PR status
69	Bradshaw (2014) USA [69]	The Long Island Breast Cancer Study Project	Female	25-91	195	1436	12.7	Breast cancer	Recreational physical activity	Post-diagnosis (MET-h/wk) 0: 1.00 0.1-9: 0.24 (0.07-0.65) >9: 0.27 (0.15-0.46)	Age, pre-diagnosis BMI, chemotherapy treatment, tumor size
70	Pelser (2014) USA [70]	NIH-AARP Diet and Health Study	Both	50-71	856	5727	5	Colorectal cancer	Recreational physical activity	Pre-diagnosis Colon Never or rarely: 1.00 1-3 time/month: 0.96 (0.76-1.22)	Lag time, sex, education, family history of colon cancer, cancer stage, first course of treatment, and

										1-2 time/wk: 0.89 (0.72-1.11) 3-5 time/wk: 0.98 (0.79-1.21) >5 times/wk: 1.16 (0.93-1.45) Rectal Never or rarely: 1.00 1-3 time/month: 1.23(0.84-1.80) 1-2 time/wk: 0.92 (0.64-1.31) 3-5 time/wk: 0.95 (0.66-1.37) >5 times/wk: 0.78 (0.53-1.15)	also mutually adjusted for quintiles of HEI-2005 scores, BMI, physical activity, alcohol, and smoking history
71	Zhou (2014) USA [71]	The Women's Health Initiative (WHI)Study	Female	50-79	301	600	10.9	Ovarian cancer	Recreational physical activity	Pre-diagnosis (MET-h/wk) Vigorous 0: 1.00 >0: 0.74 (0.56-0.98) Moderate-vigorous: 0: 1.00 0-9: 1.07 (0.79-1.44) 9-15: 0.68 (0.45-1.03) >15: 0.89 (0.65-1.23)	Age, stage, histology, time from study enrollment to ovarian cancer diagnosis, BMI, hormone therapy use, smoking, history of diabetes and status in calcium and vitamin D trial, diet modification trial, hormone therapy trial and observational study

Abbreviations: MET=Metabolic equivalents of task; BMI=body mass index

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Supplementary table S2 Dose-response relation between recreational physical activity and cancer mortality in the general population

	Number of datasets included	Recreational physical activity (MET-h/wk)						*P* for non-linearity
		0	**5**	**10**	**15**	**20**	**25**	
Overall	11	1.00	0.88(0.84-0.93)	0.86(0.82-0.90)	0.86(0.81-0.91)	0.85(0.80-0.90)	0.84(0.78-0.84)	0.006
Location								
Asia	8	1.00	0.91(0.88-0.95)	0.87(0.84-0.92)	0.86(0.81-0.91)	0.85(0.79-0.91)	0.84(0.76-0.90)	0.066
Duration of follow-up(year)								
< 10	8	1.00	0.91(0.87-0.95)	0.87(0.84-0.92)	0.86(0.83-0.92)	0.85(0.80-0.92)	0.83(0.78-0.90)	0.066
		Recreational physical activity (h/wk)						
		0	**2**	**3**	**4**	**6**	**8**	
Overall	25	1.00	0.94(0.90-0.97)	0.92(0.89-0.96)	0.91(0.88-0.95)	0.91(0.88-0.94)	0.90(0.87-0.94)	0.024
Location								
North America	20	1.00	0.93(0.89-0.96)	0.93(0.89-0.95)	0.92(0.88-0.95)	0.89(0.86-0.92)	0.94(0.92-0.95)	0.008
Duration of follow-up (year)								
⩾10	25	1.00	0.94(0.90-0.97)	0.92(0.89-0.96)	0.91(0.88-0.95)	0.91(0.88-0.94)	0.90(0.87-0.94)	0.024

[a] MET, metabolic equivalent of task.

[b] *P* value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0.

Supplementary table S3 Dose-response relation between recreational physical activity and cancer mortality among cancer survivors

	Number of datasets included	Recreational physical activity (MET-h/wk)[a]						*P*[b] for non-linearity
		0	5	10	15	30	50	
Overall	23	1.00	0.82(0.75-0.89)	0.75(0.69-0.82)	0.73(0.68-0.79)	0.70(0.63-0.77)	0.65(0.52-0.81)	<0.001
Sex								
Female	21	1.00	0.83(0.76-0.91)	0.74(0.67-0.81)	0.69(0.63-0.76)	0.71(0.61-0.84)	/	<0.001
Location								
North America	21	1.00	0.84(0.78-0.92)	0.75(0.69-0.82)	0.71(0.65-0.76)	0.69(0.62-0.76)	0.75(0.61-0.92)	<0.001
Cancer types								
Breast cancer	12	1.00	0.78(0.70-0.87)	0.68(0.61-0.76)	0.64(0.57-0.72)	0.66(0.57-0.76)	0.74(0.54-1.03)	<0.001
Colorectal cancer	8	1.00	0.89(0.76-1.02)	0.84(0.70-0.96)	0.80(0.65-0.94)	0.63(0.48-0.83)	/	0.772
When physical activity was measured								
Pre-diagnosis	14	1.00	0.82(0.74-0.91)	0.78(0.71-0.87)	0.79(0.71-0.87)	0.79(0.68-0.92)	0.79(0.57-1.12)	0.002
Post-diagnosis	11	1.00	0.80(0.71-0.92)	0.70(0.62-0.80)	0.65(0.57-0.74)	0.55(0.48-0.65)	0.53(0.38-0.75)	0.127
Duration of follow-up (year)								
< 10	21	1.00	0.82(0.74-0.89)	0.76(0.69-0.82)	0.75(0.68-0.82)	0.72(0.63-0.80)	0.67(0.53-0.86)	<0.001

[a] MET, metabolic equivalent of task.

[b] *P* value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0.