



Editor's choice
Scan to access more
free content

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

Tingting Li,¹ Shaozhong Wei,² Yun Shi,¹ Shuo Pang,¹ Qin Qin,¹ Jieyun Yin,¹ Yunte Deng,³ Qiongrong Chen,³ Sheng Wei,¹ Shaofa Nie,¹ Li Liu¹

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bjsports-2015-094927>).

¹Department of Epidemiology and Biostatistics, and the Ministry of Education Key Lab of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

²Department of Gastrointestinal Oncology, Hubei Cancer Hospital, Wuhan, Hubei, China

³Department of Pathology, Hubei Cancer Hospital, Wuhan, Hubei, China

Correspondence to

Dr Li Liu, Department of Epidemiology and Biostatistics, and the Ministry of Education Key Lab of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, No.13 of Hangkong Road, Wuhan, Hubei 430030, China gracefulliuly@163.com

TL and SW contributed equally.

Accepted 1 September 2015

Published Online First

18 September 2015



CrossMark

To cite: Li T, Wei S, Shi Y, et al. *Br J Sports Med* 2016;**50**:339–345.

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 colorectal⁴ 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 scale¹⁵ 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 I² 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 analysis²⁰ 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

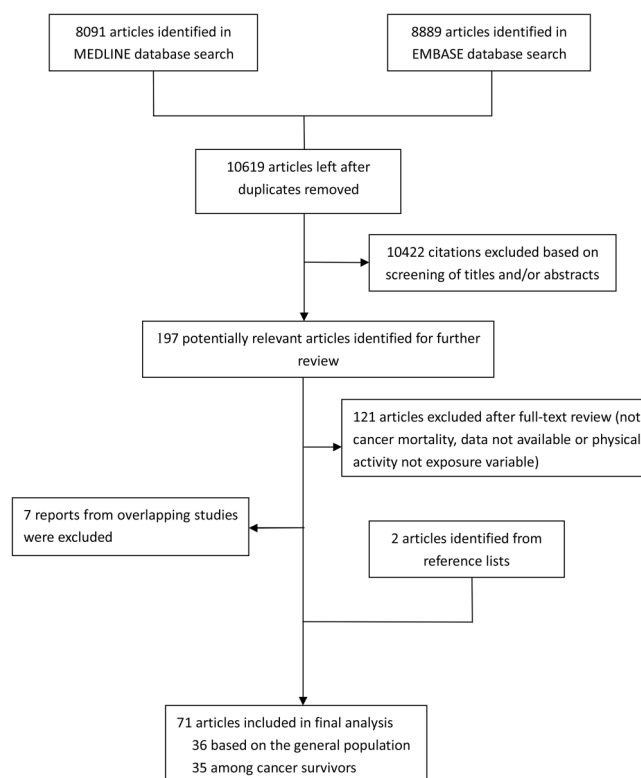


Figure 1 Flow diagram of study selection.

America,^[1 2 8 16 23 28 32 34 35] 9 in Asia^[7 12–14 25–27 31 33] and 18 in Europe.^[3–6 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,^[1–6 9 11 14–16 19 21–23 26 29–31 33 35 36] with five on colorectal cancer,^[12 24 26 27 34] four on pancreatic cancer^[18 13 18 25] and three on breast cancer.^[26 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,^[38–41 43 44 48–52 54 57–65 68–71] and six in Europe.^[45–47 53 55 67] Nineteen studies were on breast cancer survival^[37–41 44 47 50–55 57 60 61 67–69] and nine on colorectal cancer survival.^[42 43 49 56 59 62 65 66 70] Of these, 24 studies,^[37–43 45–47 51 53–55 57 61–65 67 68 70 71] 14 studies^[40 43 44 49 50 56–60 62 65 66 69] and five studies^[40 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

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.

of the most influential study (online supplementary figures S1 and S2).

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.

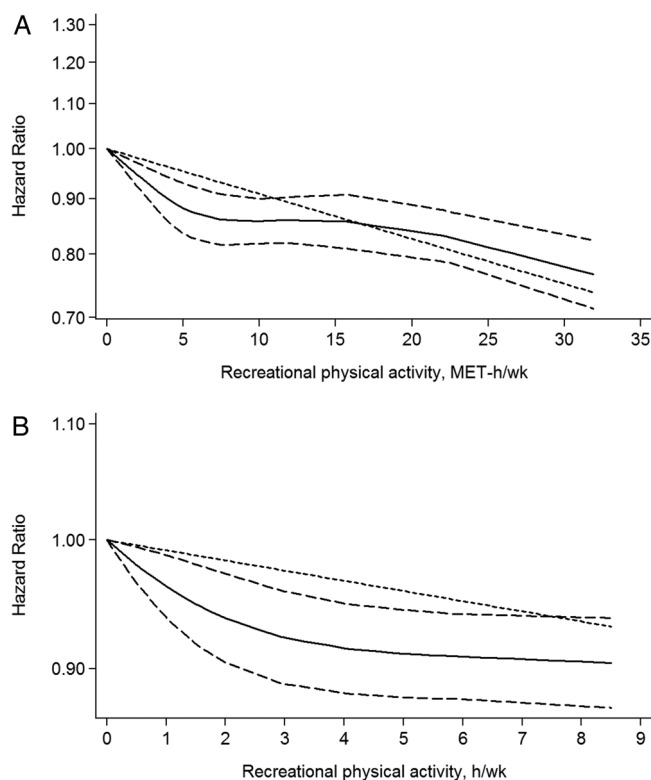


Figure 2 Dose-response relation between cancer mortality and recreational physical activity in the form of metabolic equivalents of task (MET)-h/week (A) and h/week (B) in the general population. The solid line and the long dash line represent the estimated relative risk and its 95% CI. The short dash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

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.

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).

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

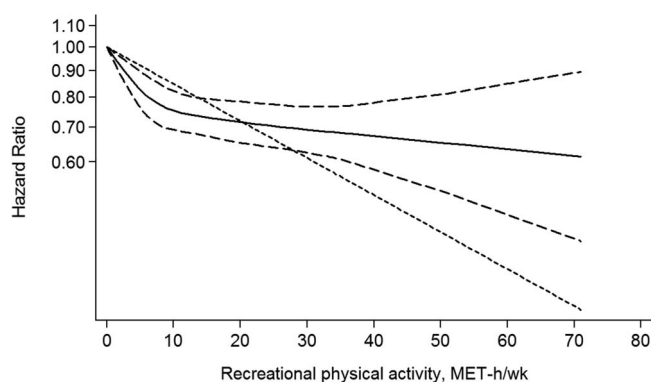


Figure 3 Dose-response relation between cancer mortality and recreational physical activity (metabolic equivalents of task (MET)-h/week) among cancer survivors. The solid line and the long dash line represent the estimated relative risk and its 95% CI. The short dash line represents the linear relationship.

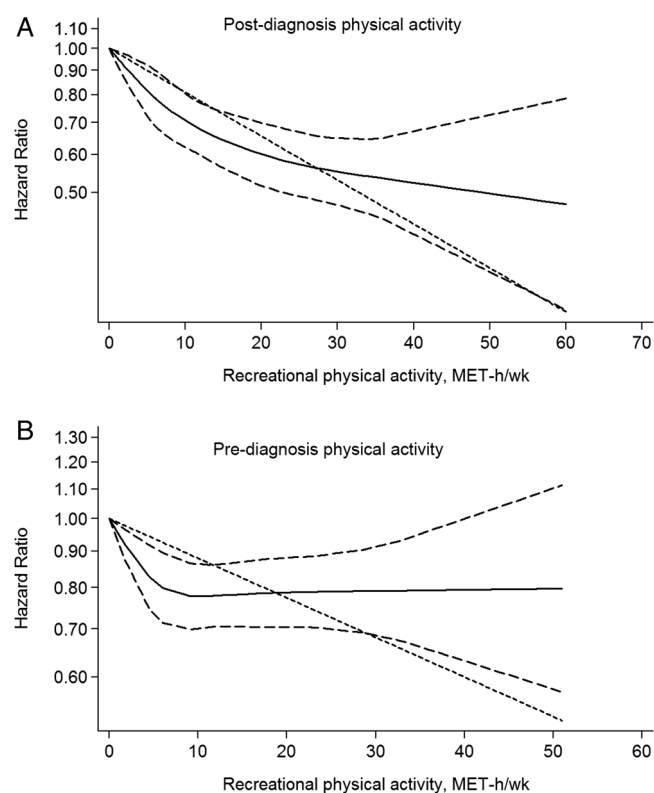


Figure 4 Dose-response relation between cancer mortality and recreational physical activity (metabolic equivalents of task (MET)-h/week) in postdiagnosis (A) and prediagnosis (B) among cancer survivors. The solid line and the long dash line represent the estimated relative risk and its 95% CI. The short 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 pre-diagnostic 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-1) 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 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.

Funding This work was supported by the National Natural Science Foundation of China (NSFC-81172754 to SW (Sheng Wei) and NSFC-81302491 to LL) and Independent Innovation Fund of Huazhong University of Science and Technology (2013QN001 to LL).

Competing interests None declared.

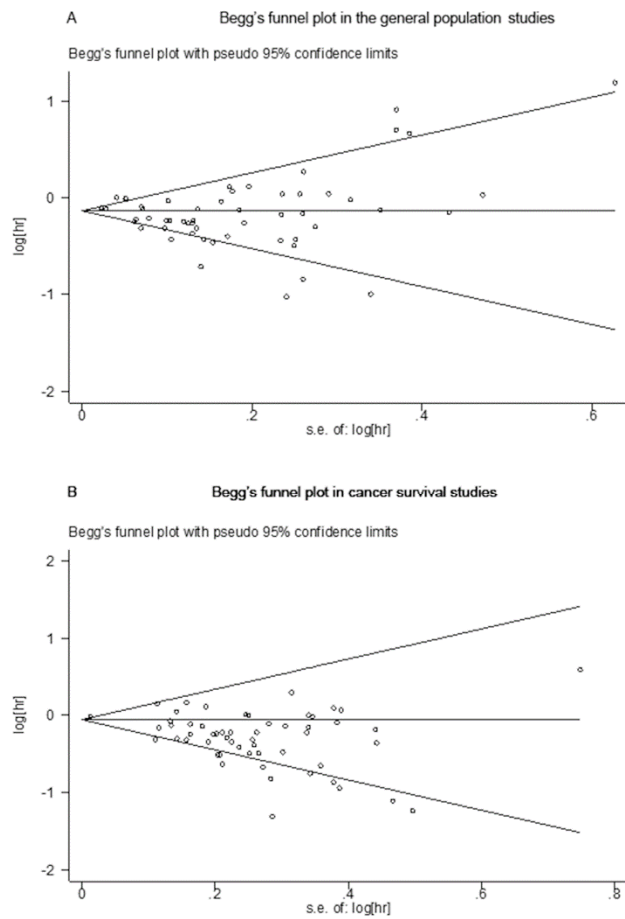
Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 World Health Organization (WHO). NCD mortality and morbidity, 2012. http://www.who.int/gho/ncd/mortality_morbidity/en/ (accessed Jan 2015).
- 2 Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. *Proc Nutr Soc* 2008;67:253–6.
- 3 Bradshaw PT, Ibrahim JG, Khankari N, et al. Post-diagnosis physical activity and survival after breast cancer diagnosis: the Long Island Breast Cancer Study. *Breast Cancer Res Treat* 2014;145:735–42.
- 4 Campbell PT, Patel AV, Newton CC, et al. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. *J Clin Oncol* 2013;31:876–85.
- 5 Kenfield SA, Stampfer MJ, Giovannucci E, et al. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol* 2011;29:726–32.
- 6 Ibrahim EM, Al-Homaidh A. Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. *Med Oncol* 2011;28:753–65.
- 7 Je Y, Jeon JY, Giovannucci EL, et al. Association between physical activity and mortality in colorectal cancer: a meta-analysis of prospective cohort studies. *Int J Cancer* 2013;133:1905–13.
- 8 World Health Organization (WHO). Global Strategy on Diet, Physical Activity and Health. http://www.who.int/dietphysicalactivity/factsheet_adults/en/ (accessed Jan 2015).
- 9 US Department of Health and Human Services. Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report. Washington DC: 2008:683. <http://www.health.gov/paguidelines/> (accessed Jan 2015).
- 10 Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32:S498–504.
- 11 Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 2007;116:1081–93.
- 12 Barbaric M, Brooks E, Moore L, et al. Effects of physical activity on cancer survival: a systematic review. *Physiother Can* 2010;62:25–34.
- 13 Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med* 2009;3:e123–30.
- 14 Wolin KY, Yan Y, Colditz GA. Physical activity and risk of colon adenoma: a meta-analysis. *Br J Cancer* 2011;104:882–5.
- 15 Cota GF, de Sousa MR, Fereguetti TO, et al. Efficacy of anti-leishmania therapy in visceral leishmaniasis among HIV infected patients: a systematic review with indirect comparison. *PLoS Negl Trop Dis* 2013;7:e2195.
- 16 Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 1985;41:55–68.
- 17 Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008;27:954–70.
- 18 Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. *Int J Epidemiol* 2011;40:1382–400.
- 19 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- 20 Sterne JA, Juni P, Schulz KF, et al. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. *Stat Med* 2002;21:1513–24.
- 21 Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000;53:1119–29.
- 22 Woodcock J, Franco OH, Orsini N, et al. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. *Int J Epidemiol* 2011;40:121–38.
- 23 Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med* 2015;175:959–67.
- 24 Zhong S, Jiang T, Ma T, et al. Association between physical activity and mortality in breast cancer: a meta-analysis of cohort studies. *Eur J Epidemiol* 2014;29:391–404.
- 25 US Department of Health and Human Services. *Physical activity guidelines for Americans*. Washington DC: US Department of Health and Human Services, 2008.
- 26 Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer* 2010;46:2593–604.
- 27 Bradley RL, Jeon JY, Liu FF, et al. Voluntary exercise improves insulin sensitivity and adipose tissue inflammation in diet-induced obese mice. *Am J Physiol Endocrinol Metab* 2008;295:E586–94.
- 28 Chu SH, Park JH, Lee MK, et al. The association between pentraxin 3 and insulin resistance in obese children at baseline and after physical activity intervention. *Clin Chim Acta* 2012;413:1430–7.
- 29 Kim ES, Im JA, Kim KC, et al. Improved insulin sensitivity and adiponectin level after exercise training in obese Korean youth. *Obesity (Silver Spring)* 2007;15:3023–30.
- 30 Helmrich SP, Ragland DR, Leung RW, et al. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 1991;325:147–52.
- 31 Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst* 2000;92:1592–600.
- 32 Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst* 1999;91:620–5.
- 33 Giovannucci E, Pollak MN, Platz EA, et al. A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers Prev* 2000;9:345–9.
- 34 Trevisan M, Liu J, Muti P, et al. Markers of insulin resistance and colorectal cancer mortality. *Cancer Epidemiol Biomarkers Prev* 2001;10:937–41.
- 35 Mulligan AM, O'Malley FP, Ennis M, et al. Insulin receptor is an independent predictor of a favorable outcome in early stage breast cancer. *Breast Cancer Res Treat* 2007;106:39–47.
- 36 Boyle P, Boniol M, Koechlin A, et al. Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer* 2012;107:1608–17.
- 37 McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer* 2008;8:205–11.
- 38 Irwin ML, Varma K, Alvarez-Reeves M, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. *Cancer Epidemiol Biomarkers Prev* 2009;18:306–13.
- 39 Ligibel JA, Campbell N, Partridge A, et al. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. *J Clin Oncol* 2008;26:907–12.
- 40 Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol* 2014;25:1293–311.

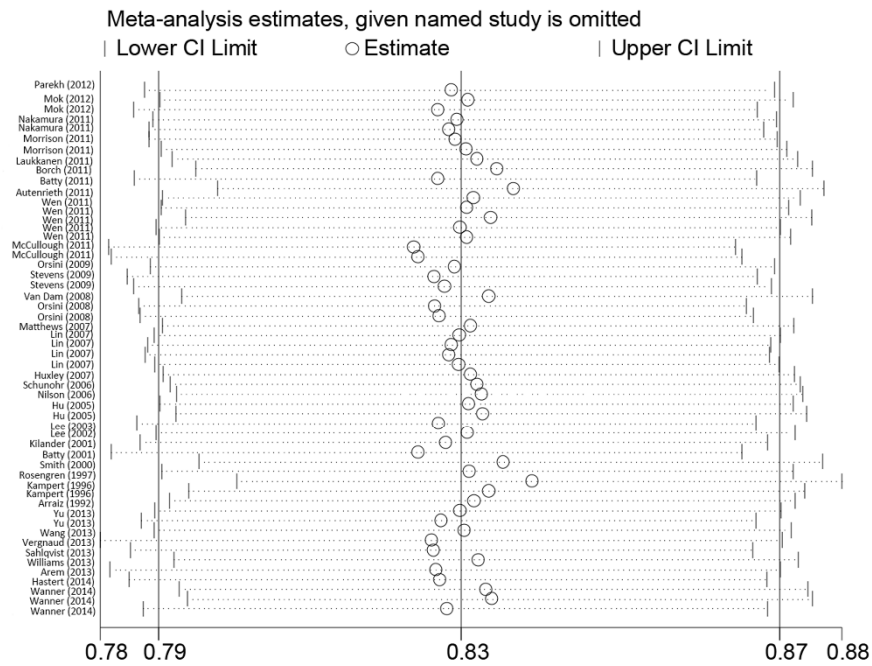
- 41 Meyerhardt JA, Giovannucci EL, Holmes MD, *et al.* Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006;24:3527–34.
- 42 Irwin ML, McTiernan A, Manson JE, *et al.* Physical activity and survival in postmenopausal women with breast cancer: results from the women's health initiative. *Cancer Prev Res (Phila)* 2011;4:522–9.
- 43 Stevinson C, Lawlor DA, Fox KR. Exercise interventions for cancer patients: systematic review of controlled trials. *Cancer Causes Control* 2004;15:1035–56.
- 44 Knols R, Aaronson NK, Uebelhart D, *et al.* Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. *J Clin Oncol* 2005;23:3830–42.
- 45 Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol* 2005;23:899–909.
- 46 Schmitz KH, Courneya KS, Matthews C, *et al.* American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;42:1409–26.
- 47 Wiggins MS, Simonavice EM. Cancer prevention, aerobic capacity, and physical functioning in survivors related to physical activity: a recent review. *Cancer Manag Res* 2010;2:157–64.
- 48 Meyerhardt JA, Giovannucci EL, Ogino S, *et al.* Physical activity and male colorectal cancer survival. *Arch Intern Med* 2009;169:2102–8.

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.

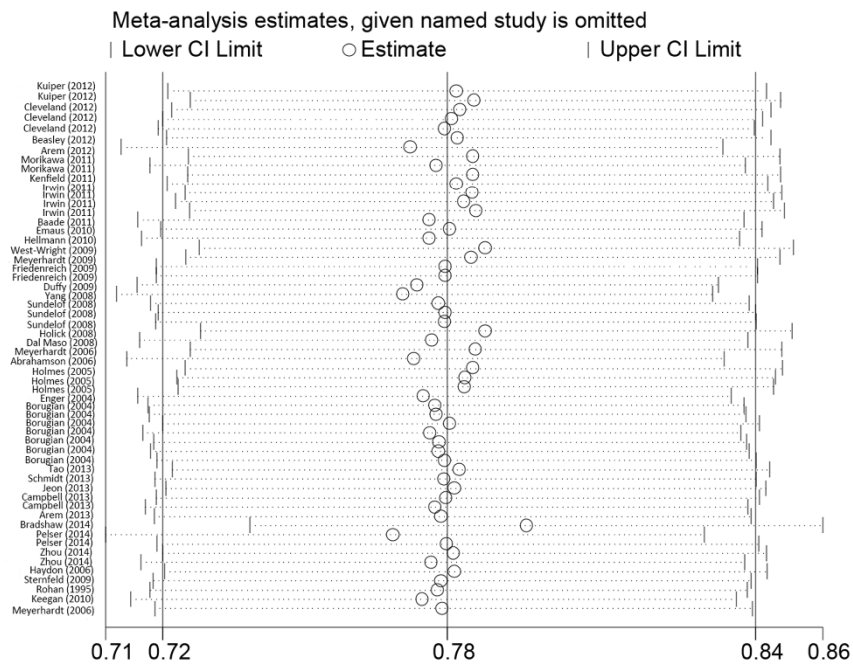


Supplementary figure S2 Sensitivity analyses for the association between physical activity and cancer mortality in the general population studies (A) and in cancer survival studies (B).

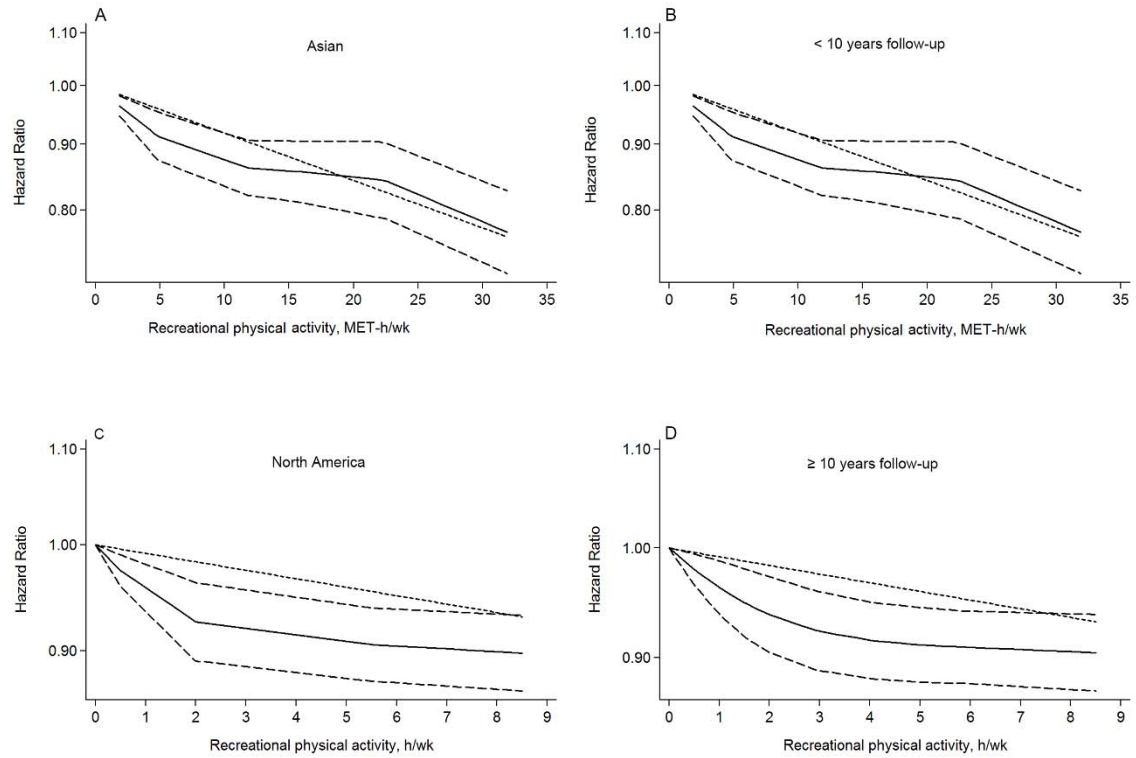
A Sensitivity analysis in the general population studies



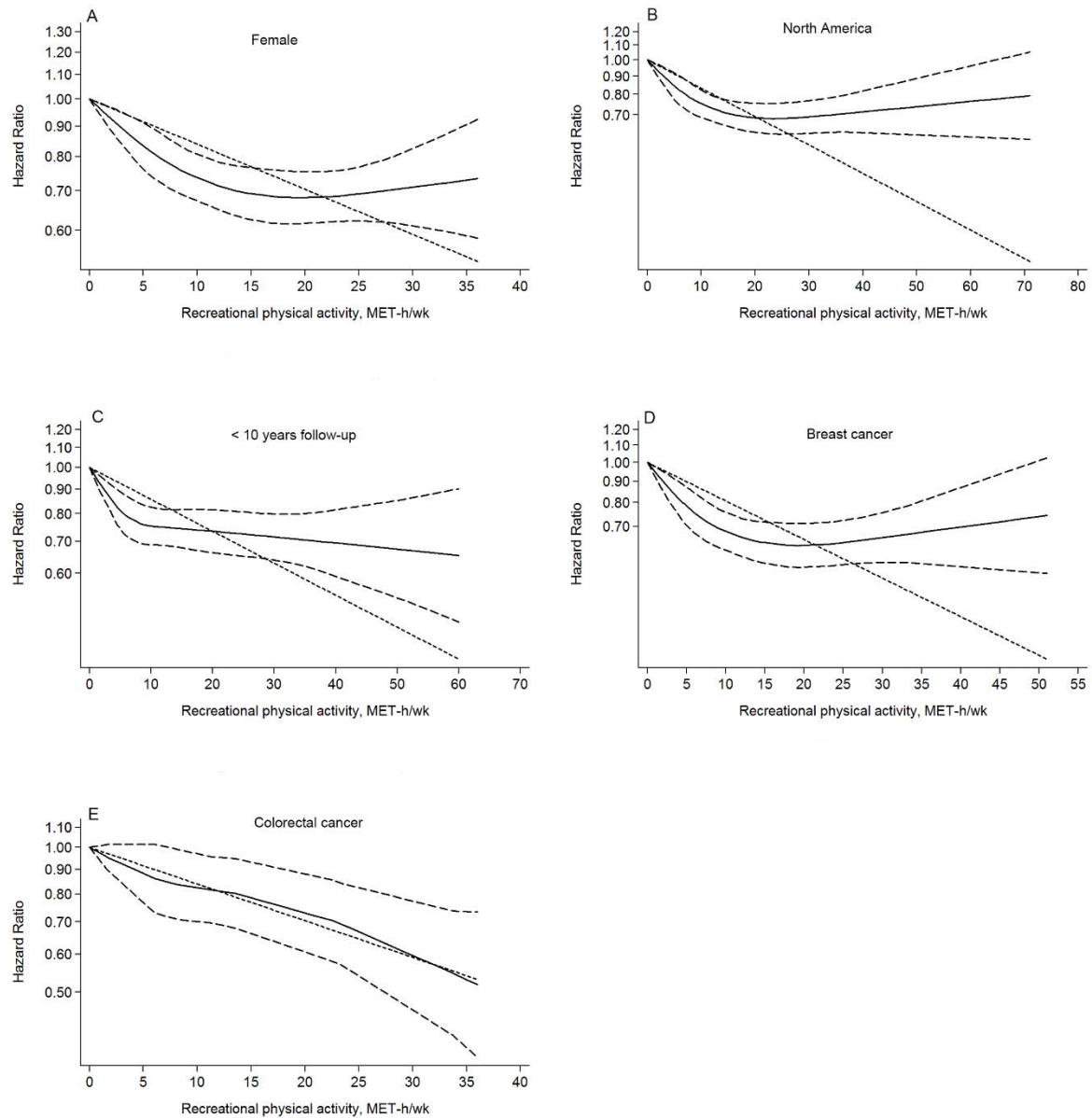
B Sensitivity analysis in cancer survival studies



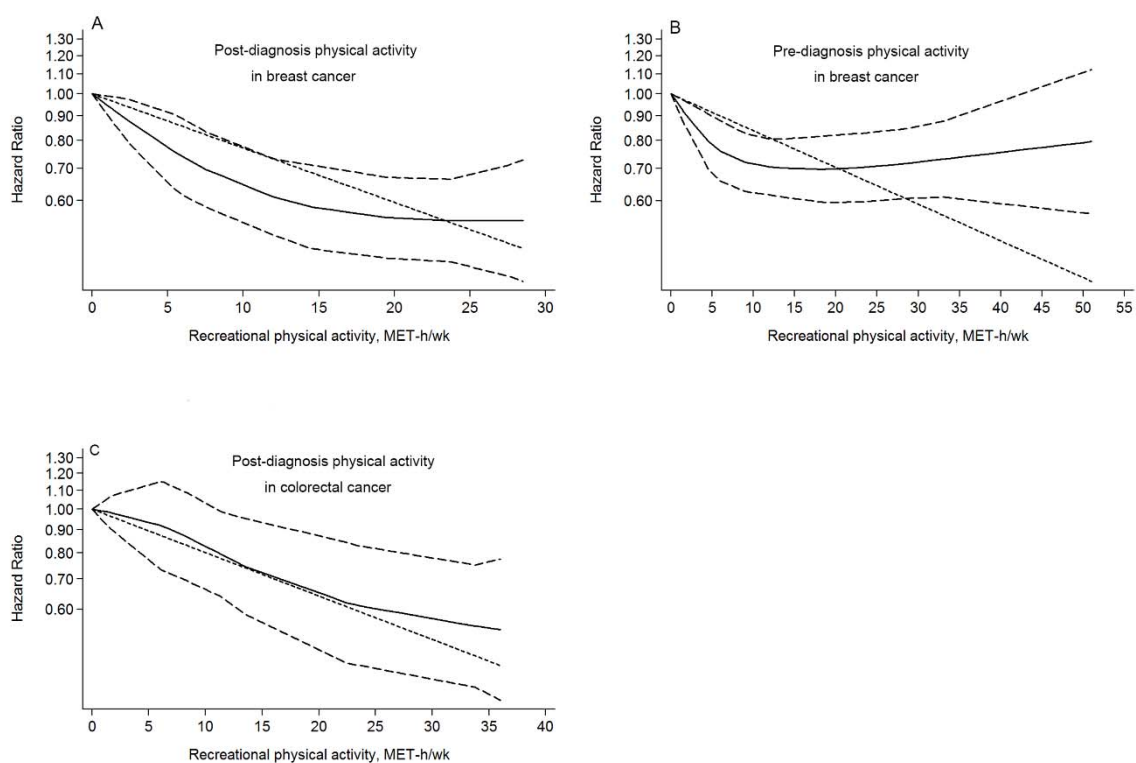
Supplementary figure S3 Dose-response analysis between cancer mortality and recreational physical activity in the general population in the subgroup of Asian (A), < 10 years follow-up (B), North America (C) and ≥ 10 years follow-up (D). The solid line and the long dash line represent the estimated relative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



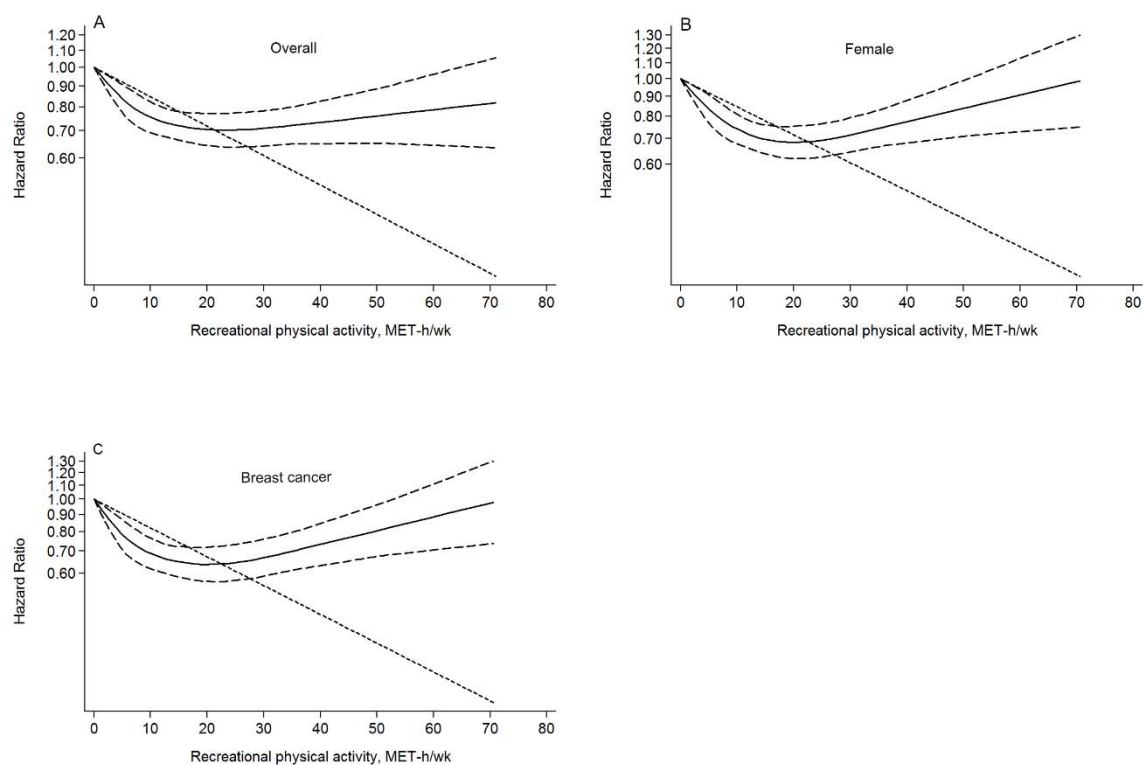
Supplementary figure S4 Dose-response analysis between cancer mortality and recreational physical activity among cancer survivors in the subgroup of female (A), North America (B), ≥ 10 years follow-up (C), breast cancer (D) and colorectal cancer (E). The solid line and the long dash line represent the 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) (Mean ± SD)s	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	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 activity	physical	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 activity	physical	(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 activity	physical	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 activity	physical	(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 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 activity	physical	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 activity	physical (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 activity	physical (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 activity	physical (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 activity	physical 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 activity	physical 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 activity	physical	(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 activity	physical	(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 activity	physical	(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 (Female)	51	30826	212247 (person-years)	Pancreatic cancer	Recreational activity	physical	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 activity	physical	(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 activity	physical	(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 activity	physical	(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 activity	physical	(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. 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
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)	Follow-up age, race, menopause, oral contraceptive and estrogen/progesterone use, BMI
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)	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
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) Strenuous/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) Strenuous/muscle-conditioning Inactive: 1.00 Active: 0.93 (0.29-2.95)	
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	eating index 2010 score, calories, marriage status, diabetes and smoke level
		<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)	

>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 activity	physical	<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 tremuous 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
												Age, educational level, marital status, survey, smoking and nutrition
36	Wanner (2014) Switzerland ³⁶	The National Research Program 1A and Swiss MONICA study	Both	16-92	1351	17663	20.2	All	Recreational activity	physical	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)	
37	Rohan (1995) Austria ³⁷	A population-based cohort of breast cancer patients	Female	20-74	112	411	5.5	Breast cancer	Recreational activity	physical	(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 activity	physical	(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 activity	physical	(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,	

41	Abrahamson (2006) USA ⁴¹	A follow-up study	Female	20-54	212	1264	8.5	Breast cancer	Recreational activity	physical	15-23.9: 0.44 (0.21-0.93) ≥24: 0.52 (0.26-1.06) (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) Australia ⁴²	The Melbourne Collaborative Cohort Study (MCCS)	Both	25-75	181	526	5.5	Colorectal cancer	Recreational activity	physical	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 activity	physical	(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 activity	physical	(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 activity	physical	Pre-diagnosis Oesophageal adenocarcinoma 1 st (low): 1.00 2 nd : 0.90 (0.50-1.50)	Age, sex, education, symptomatic gastroesophageal reflux, BMI, tobacco smoking.

		(SECC study)						squamous-cell carcinoma, Gastric cardia adenocarcinoma				3 rd : 0.70 (0.40-1.20) 4 th (high): 0.90 (0.50-1.50) Oesophageal squamous-cell carcinoma 1 st (low): 1.00 2 nd : 1.00 (0.60-1.70) 3 rd : 0.90 (0.50-1.60) 4 th (high): 0.80 (0.40-1.50) Gastric cardia adenocarcinoma 1 st (low): 1.00 2 nd : 0.90 (0.60-1.40) 3 rd : 1.00 (0.70-1.50) 4 th (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 activity	physical	(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 activity	physical	(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 activity	physical	(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 activity	physical	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 activity	physical	(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 (0.47-1.04) 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 activity	physical	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 activity	physical	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 activity	physical	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) Australia ⁵⁶	A longitudinal study	Both	21-82	345	1825	4.9	Colorectal cancer	Recreational activity	physical	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 activity	physical	(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 0.1-3.0: 0.91 (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	

58	Kenfield (2011) USA ⁵⁸	The Health Professionals Follow-Up Study	Male	/	112	2705	9.7	Prostate cancer	Recreational activity	physical	3.1-8.9: 0.71 (0.42-1.20) ≥9: 0.51 (0.30-0.87) 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	1128 2		Breast cancer	Recreational activity	physical	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 activity	physical	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 activity	physical	(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 activity	physical	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 activity	physical	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 activity	physical	(MET-h/wk) Pre-diagnosis <3.5: 1.00	Age at diagnosis, sex, smoking status, body mass index, red meat

66	Jeon (2013) National ⁶⁶	GALGB	Female	/	169	237	7.3	Colorectal cancer	Recreational activity	physical	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) Post-diagnosis (MET-h/wk) <3: 1.00 3-17.9: 0.85 (0.58-1.23) ≥18: 0.71 (0.46-1.11)	intake, Surveillance, Epidemiology, and End Results (SEER) summary stage at diagnosis, leisure-time spent sitting, and education 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 activity	physical	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 activity	physical	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 activity	physical	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

- 7 Lee SY, Kim MT, Jee SH, *et al.* Does hypertension increase mortality risk from lung cancer? A prospective cohort study on smoking, hypertension and lung cancer risk among Korean men. *J Hypertens* 2002 20:617-22.
- 8 Lee IM, Sesso HD, Oguma Y, *et al.* Physical activity, body weight, and pancreatic cancer mortality. *Br J Cancer* 2003;88:679-83.
- 9 Hu G, Tuomilehto J, Silventoinen K, *et al.* The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged Finnish men and women. *Int J Obes (Lond)* 2005;29:894-902.
- 10 Nilsen TI, Romundstad PR, Vatten LJ. Recreational physical activity and risk of prostate cancer: A prospective population-based study in Norway (the HUNT study). *Int J Cancer* 2006;119:2943-7.
- 11 Schnohr P, Lange P, Scharling H, *et al.* Long-term physical activity in leisure time and mortality from coronary heart disease, stroke, respiratory diseases, and cancer. The Copenhagen City Heart Study. *Eur J Cardiovasc Prev Rehabil* 2006;13:173-9.
- 12 Huxley R. The role of lifestyle risk factors on mortality from colorectal cancer in populations of the Asia-Pacific region. *Asian Pac J Cancer Prev* 2007;8:191-8.
- 13 Lin Y, Kikuchi S, Tamakoshi A, *et al.* Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort. *Int J Cancer* 2007;120:2665-71.
- 14 Matthews CE, Jurj AL, Shu XO, *et al.* Influence of exercise, walking, cycling, and overall nonexercise physical activity on mortality in Chinese women. *Am J Epidemiol* 2007;165:1343-50.
- 15 Orsini N, Bellocco R, Bottai M, *et al.* Combined effects of obesity and physical activity in predicting mortality among men. *J Intern Med* 2008 264:442-51.
- 16 van Dam RM, Li T, Spiegelman D, *et al.* Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *BMJ* 2008 337:a1440.
- 17 Orsini N, Bellocco R, Bottai M, *et al.* A prospective study of lifetime physical activity and prostate cancer incidence and mortality. *Br J Cancer* 2009;101:1932-8.
- 18 Stevens RJ, Roddam AW, Spencer EA, *et al.* Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. *Int J Cancer* 2009 124:2400-5.
- 19 Autenrieth CS, Baumert J, Baumeister SE, *et al.* Association between domains of physical activity and all-cause, cardiovascular and cancer mortality. *Eur J Epidemiol* 2011;26:91-9.
- 20 Batty GD, Kivimaki M, Clarke R, *et al.* Modifiable risk factors for prostate cancer mortality in London: forty years of follow-up in the Whitehall study. *Cancer Causes Control* 2011;22:311-8.
- 21 Borch KB, Braaten T, Lund E, *et al.* Physical activity and mortality among Norwegian women - the Norwegian Women and Cancer Study. *Clin Epidemiol* 2011;3:229-35.
- 22 Laukkanen JA, Rauramaa R, Makikallio TH, *et al.* Intensity of leisure-time physical activity and cancer mortality in men. *Br J Sports Med* 2011;45:125-9.
- 23 McCullough ML, Patel AV, Kushi LH, *et al.* Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. *Cancer*

Epidemiol Biomarkers Prev 2011;20:1089-97.

- 24 Morrison DS, Batty GD, Kivimaki M, *et al.* Risk factors for colonic and rectal cancer mortality: evidence from 40 years' follow-up in the Whitehall I study. *J Epidemiol Community Health* 2011;65:1053-8.
- 25 Nakamura K, Nagata C, Wada K, *et al.* Cigarette smoking and other lifestyle factors in relation to the risk of pancreatic cancer death: a prospective cohort study in Japan. *Jpn J Clin Oncol* 2011;41:225-31.
- 26 Wen CP, Wai JP, Tsai MK, *et al.* Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011;378:1244-53.
- 27 Mok Y, Won S, Kimm H, *et al.* Physical Activity Level and Risk of Death: The Severance Cohort Study. *J Epidemiol* 2012.
- 28 Parekh N, Lin Y, Craft LL, *et al.* Longitudinal associations of leisure-time physical activity and cancer mortality in the Third National Health and Nutrition Examination Survey (1986-2006). *J Obes* 2012;2012:518358.
- 29 Sahlqvist S, Goodman A, Simmons RK, *et al.* The association of cycling with all-cause, cardiovascular and cancer mortality: findings from the population-based EPIC-Norfolk cohort. *BMJ Open* 2013;3:e003797.
- 30 Vergnaud AC, Romaguera D, Peeters PH, *et al.* Adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines and risk of death in Europe: results from the European Prospective Investigation into Nutrition and Cancer cohort study1,4. *Am J Clin Nutr* 2013;97:1107-20.
- 31 Wang N, Zhang X, Xiang YB, *et al.* Associations of Tai Chi, walking, and jogging with mortality in Chinese men. *Am J Epidemiol* 2013;178:791-6.
- 32 Williams PT. Breast cancer mortality vs. exercise and breast size in runners and walkers. *PLoS One* 2013;8:e80616.
- 33 Yu R, Leung J, Woo J. Housework reduces all-cause and cancer mortality in Chinese men. *PLoS One* 2013;8:e61529.
- 34 Arem H, Moore SC, Park Y, *et al.* Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. *Int J Cancer* 2014;135:423-31.
- 35 Hastert TA, Beresford SA, Sheppard L, *et al.* Adherence to the WCRF/AICR cancer prevention recommendations and cancer-specific mortality: results from the Vitamins and Lifestyle (VITAL) Study. *Cancer Causes Control* 2014;25:541-52.
- 36 Wanner M, Tarnutzer S, Martin BW, *et al.* Impact of different domains of physical activity on cause-specific mortality: a longitudinal study. *Prev Med* 2014;62:89-95.
- 37 Rohan TE, Fu W, Hiller JE. Physical activity and survival from breast cancer. *Eur J Cancer Prev* 1995;4:419-24.
- 38 Enger SM, Bernstein L. Exercise activity, body size and premenopausal breast cancer survival. *Br J Cancer* 2004;90:2138-41.
- 39 Borugian MJ, Sheps SB, Kim-Sing C, *et al.* Insulin, macronutrient intake, and physical activity: are potential indicators of insulin resistance associated with mortality from breast cancer? *Cancer Epidemiol Biomarkers Prev* 2004 13:1163-72.
- 40 Holmes MD, Chen WY, Feskanich D, *et al.* Physical activity and survival after breast cancer diagnosis. *JAMA* 2005 293:2479-86.

- 41 Abrahamson PE, Gammon MD, Lund MJ, *et al.* Recreational physical activity and survival among young women with breast cancer. *Cancer* 2006;107:1777-85.
- 42 Haydon AM, Macinnis RJ, English DR, *et al.* Effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut* 2006;55:62-7.
- 43 Meyerhardt JA, Giovannucci EL, Holmes MD, *et al.* Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006;24:3527-34.
- 44 Holick CN, Newcomb PA, Trentham-Dietz A, *et al.* Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:379-86.
- 45 Sundelof M, Lagergren J, Ye W. Patient demographics and lifestyle factors influencing long-term survival of oesophageal cancer and gastric cardia cancer in a nationwide study in Sweden. *Eur J Cancer* 2008;44:1566-71.
- 46 Yang L, Klint A, Lambe M, *et al.* Predictors of ovarian cancer survival: a population-based prospective study in Sweden. *Int J Cancer* 2008;123:672-9.
- 47 Dal Maso L, Zucchetto A, Talamini R, *et al.* Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *Int J Cancer* 2008;123:2188-94.
- 48 Duffy SA, Ronis DL, McLean S, *et al.* Pretreatment health behaviors predict survival among patients with head and neck squamous cell carcinoma. *J Clin Oncol* 2009;27:1969-75.
- 49 Meyerhardt JA, Giovannucci EL, Ogino S, *et al.* Physical activity and male colorectal cancer survival. *Arch Intern Med* 2009;169:2102-8.
- 50 Sternfeld B, Weltzien E, Quesenberry CP, Jr., *et al.* Physical activity and risk of recurrence and mortality in breast cancer survivors: findings from the LACE study. *Cancer Epidemiol Biomarkers Prev* 2009;18:87-95.
- 51 West-Wright CN, Henderson KD, Sullivan-Halley J, *et al.* Long-term and recent recreational physical activity and survival after breast cancer: the California Teachers Study. *Cancer Epidemiol Biomarkers Prev* 2009;18:2851-9.
- 52 Friedenreich CM, Gregory J, Kopciuk KA, *et al.* Prospective cohort study of lifetime physical activity and breast cancer survival. *Int J Cancer* 2009;124:1954-62.
- 53 Hellmann SS, Thygesen LC, Tolstrup JS, *et al.* Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. *Eur J Cancer Prev* 2010;19:366-73.
- 54 Keegan TH, Milne RL, Andrulis IL, *et al.* Past recreational physical activity, body size, and all-cause mortality following breast cancer diagnosis: results from the Breast Cancer Family Registry. *Breast Cancer Res Treat* 2010;123:531-42.
- 55 Emaus A, Veierod MB, Tretli S, *et al.* Metabolic profile, physical activity, and mortality in breast cancer patients. *Breast Cancer Res Treat* 2010;121:651-60.
- 56 Baade PD, Meng X, Youl PH, *et al.* The impact of body mass index and physical activity on mortality among patients with colorectal cancer in Queensland, Australia. *Cancer Epidemiol Biomarkers Prev* 2011;20:1410-20.
- 57 Irwin ML, McTiernan A, Manson JE, *et al.* Physical activity and survival in postmenopausal women with breast cancer: results from the women's health initiative. *Cancer Prev Res (Phila)* 2011;4:522-9.

- 58 Kenfield SA, Stampfer MJ, Giovannucci E, *et al.* Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol* 2011;29:726-32.
- 59 Morikawa T, Kuchiba A, Yamauchi M, *et al.* Association of CTNNB1 (beta-catenin) alterations, body mass index, and physical activity with survival in patients with colorectal cancer. *JAMA* 2011;305:1685-94.
- 60 Beasley JM, Kwan ML, Chen WY, *et al.* Meeting the physical activity guidelines and survival after breast cancer: findings from the after breast cancer pooling project. *Breast Cancer Res Treat* 2012;131:637-43.
- 61 Cleveland RJ, Eng SM, Stevens J, *et al.* Influence of prediagnostic recreational physical activity on survival from breast cancer. *Eur J Cancer Prev* 2012;21:46-54.
- 62 Kuiper JG, Phipps AI, Neuhaus ML, *et al.* Recreational physical activity, body mass index, and survival in women with colorectal cancer. *Cancer Causes Control* 2012.
- 63 Arem H, Chlebowski R, Stefanick ML, *et al.* Body mass index, physical activity, and survival after endometrial cancer diagnosis: results from the Women's Health Initiative. *Gynecol Oncol* 2013;128:181-6.
- 64 Arem H, Park Y, Peller C, *et al.* Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. *J Natl Cancer Inst* 2013;105:342-9.
- 65 Campbell PT, Patel AV, Newton CC, *et al.* Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. *J Clin Oncol* 2013;31:876-85.
- 66 Jeon J, Sato K, Niedzwiecki D, *et al.* Impact of Physical Activity After Cancer Diagnosis on Survival in Patients With Recurrent Colon Cancer: Findings From CALGB 89803/Alliance. *Clin Colorectal Cancer* 2013.
- 67 Schmidt ME, Chang-Claude J, Vrieling A, *et al.* Association of pre-diagnosis physical activity with recurrence and mortality among women with breast cancer. *Int J Cancer* 2013;133:1431-40.
- 68 Tao MH, Hainaut P, Marian C, *et al.* Association of prediagnostic physical activity with survival following breast cancer diagnosis: influence of TP53 mutation status. *Cancer Causes Control* 2013.
- 69 Bradshaw PT, Ibrahim JG, Khankari N, *et al.* Post-diagnosis physical activity and survival after breast cancer diagnosis: the Long Island Breast Cancer Study. *Breast Cancer Res Treat* 2014;145:735-42.
- 70 Peller C, Arem H, Pfeiffer RM, *et al.* Prediagnostic lifestyle factors and survival after colon and rectal cancer diagnosis in the National Institutes of Health (NIH)-AARP Diet and Health Study. *Cancer* 2014;120:1540-7.
- 71 Zhou Y, Chlebowski R, LaMonte MJ, *et al.* Body mass index, physical activity, and mortality in women diagnosed with ovarian cancer: results from the Women's Health Initiative. *Gynecol Oncol* 2014;133:4-10.

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)						<i>P</i> 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						<i>P</i> ^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.