**Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770,000 cancer cases.**

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**ABSTRACT**

**Objective:** To provide an overview of the breadth and validity of claimed associations between physical activity and risk of developing or dying from cancer.

**Design:** Umbrella review.

**Data Sources:** We searched Medline, Embase, Cochrane Database, and Web of Science.

**Eligibility criteria for selecting studies:** Systematic reviews about physical activity and cancer incidence and cancer mortality in different body sites among general population.

**Results**: We included nineteen reviews covering 22 cancer sites, 26 exposure-outcome pairs comparisons, and 541 original studies. Physical activity was associated with lower risk of seven cancer sites (colon, breast, endometrial, lung, esophageal, pancreas, and meningioma). Only colon (a protective association with recreational physical activity) and breast cancer (a protective association with overall physical activity) were supported by strong evidence and highly suggestive evidence, respectively. Evidence from endometrial, lung, esophageal, pancreas, and meningioma presented hints of uncertainty and bias in the literature (*e.g.*, not reaching P values <10-6), showing large between-study heterogeneity, and/or not demonstrating a definite direction for the effect when 95% prediction intervals were considered). Four of the 26 meta-analyses showed small study effects and 4 showed excess significance.

**Conclusion:** Physical activity is associated with a lower risk of several cancers, but only colon and breast cancer associations were supported by strong or highly suggestive evidence, respectively. Evidence from other cancer sites was less consistent, presenting hints of uncertainty and/or bias.

What is already known:

**-** Physical activity has been traditionally linked with lower risks of breast and colon cancer

- Recently, multiple meta-analyses have showed that physical activity might be additionally associated with lower risk of several other cancer sites.

- If these associations are causal, a substantial burden of cancer could be avoided worldwide, but it is also plausible that some associations may be flawed due to biases in the literature.

What are the new findings:

- This umbrella review synthesizes and evaluates the robustness of evidence and appraises uncertainty and bias in the body of literature of the association between physical activity and the risk of developing or dying from cancer.

- Of the 22 major anatomical cancer sites included in our primary analysis, only colon cancer and breast cancer were supported by strong or highly suggestive evidence.

- Evidence from other cancer sites was less consistent, presenting hints of uncertainty and bias in the literature.

**INTRODUCTION**

Physical activity has been traditionally linked with lower risks of colon and breast cancer.1-6 Annually, thousands of new epidemiological studies are conducted and published to examine whether physical activity may also decrease risk of other types of cancer. Recently, prospective cohort studies7,8 and meta-analyses have claimed that physical activity might be additionally associated with cancer of bladder,9 endometrial,10 esophageal,11 gastric,12 glioma,13 kidney,14 lung,15 meningioma,13 ovarian,16 pancreas,17 and prostate.18 If these associations are causal, a substantial burden of cancer could be avoided worldwide given the high prevalence of physical inactivity.19

Another possibility is that some claimed associations about physical activity and cancer could be explained by biases in the literature. There is strong evidence that studies showing positive and significant results are more likely to be published than studies with negative and non-significant findings.20 These sorts of publication bias and outcome reporting bias threat validity of scientific evidence.21,22 causes general public anxiety and skepticism,23 and misguide clinical and public health decisions. In fact, bias has been suspected in cancer epidemiology literature about presumed risk and prognostic factors, biomarkers, and multiple carcinogens.24-31 Nevertheless, neither the international organizations (*e.g.*, International Agency for Research on Cancer – IARC; World Cancer Research Fund – WCRF)2,32 nor the most comprehensive systematic reviews and meta-analyses on physical activity and cancer have considered the array of analytical procedures available to detect hints of uncertainty and bias in the body of evidence to state their conclusions (Table S1).

We performed an umbrella review26,27,30,31,33 of systematic reviews and meta-analyses to provide an overview of the breadth and validity of claimed association between physical activity and risk of developing or dying from cancer. We comprehensively evaluated the robustness of evidence between physical activity and cancer, appraising hints of uncertainty and bias in the body of literature.

**METHODS**

**Literature Search**

We searched Medline, Embase, Cochrane Database of systematic reviews, and Web of Science for systematic reviews published up to 22th November 2016, aiming to investigate the association between physical activity and risk of cancer incidence and cancer mortality. Table S2 in the appendix shows the search strategy. We also reviewed the references list of the eligible reviews.

**Selection of reviews and methodological quality assessment**

We only selected systematic reviews (irrespective of performing meta-analyses) evaluating the association between physical activity and cancer among the general (healthy) population. Whenever more than one eligible systematic review addressed the association between physical activity and the same cancer site, we selected the review with the largest number of studies included. We selected more than one review per cancer site whenever the reviews with the largest number of individual studies were restricted by study design or cancer subsite. In these cases (*i.e.*, breast, colon, and rectum cancers), data analyses were performed separated by review to avoid overlap of studies. We excluded systematic reviews of prognostic studies, reviews that did not systematically search the literature, and reviews that did not provided comprehensive data from individual studies (specifically information listed in the data extraction section). Two researchers (LFMR and JPRL) independently selected the eligible reviews after screening consequently titles, abstracts and full texts. A third researcher (THS) settled disagreements between authors. The list of included and excluded reviews is available in the Table S3 in the appendix.

We assessed the methodological quality of the included reviews using the AMSTAR tool34 and gathering data on statistical analyses used to assess hints of uncertainty and bias in the body of evidence.

**Data extraction**

We extracted author’s name, year of publication, number of studies included (by study design), physical activity domains (*e.g.*, recreational, occupational, total), and maximally-adjusted summary estimates from the systematic reviews. For each individual study in a systematic review, we extracted authors, year of publication, study design (case-control or cohort), sex, physical activity domain, period in life which of physical activity was measured, number of cases and controls (for case-control studies), number of cases and sample size (for cohort studies), cancer indicator (incidence, mortality, or incidence and mortality), maximally-adjusted measure of association and its respective 95% confidence intervals (95% CI) comparing high versus low categories of physical activity. Data extraction was independently performed by two researchers (LFMR and JPRL), with discrepancies solved by a third researcher (THS).

**Statistical analysis**

*Primary analysis*

The primary analysis in this umbrella review focused on two approaches to evaluate the association between physical activity and cancer. 1) ‘Any physical activity’: if individual study presented multiple measures of association by physical activity domains, we selected one based on the following order: total physical activity, multiple physical activity domains, recreational, commuting, occupational, and household physical activity. We considered ‘total physical activity’ any estimate with all four physical activity domains, and ‘multiple physical activity’ an estimate with a combination of at least two, but not all, domains. The ‘any physical activity’ approach was the most comprehensive analysis since it included the largest number of estimates per meta-analysis; 2) Recreational physical activity: we performed data analysis using all individual studies presenting recreational physical activity estimates. Recreational physical activity is the most studied and the more easily modifiable physical activity in comparison to other domains.

Both approaches used in the primary analysis included only cohort studies (i.e. case-control results were considered in the stratified and subgroup analyses) and one measure of association per individual study. Whenever a measure of association was not available for the total sample in an individual study (*e.g.*, men and women relative risks [RR] estimates were provided separately), we performed fixed effect models to estimate summary effects between categories, and included the latter in the meta-analysis. In addition, one systematic review17 presented multiple estimates based on timing in life measures for the same physical activity domain (*e.g.*, distant past, recent, consistent over time) and we selected the consistent over time measure (same criteria used by the authors17).

*Stratified and subgroup analyses*

We also performed stratified analyses combining estimates by study design (case-control and all study design – cohort and case-control), sex, and other physical activity domains (*e.g.*, total physical activity, occupational physical activity) within and across studies. In addition, considering all study designs, we re-performed subgroup analysis conducted in the original meta-analyses.

*Estimation of summary effect*

We standardized the least active category as reference group across meta-analyses and then performed the meta-analysis of physical activity (*i.e.*, high vs low category) and each cancer site according to cancer indicators. We estimated summary effect measures and its 95% confidence intervals using random effect models.

*Heterogeneity between studies*

Heterogeneity between studies was estimated using the I2 measure of inconsistency35,36 and 95% prediction intervals. The 95% prediction interval accounts for heterogeneity between studies and represents the range in which a future study will lie.37

*Small study effect and excess significance biases*

Bias in the body of evidence was assessed by small study effect and excess significance tests. The presence of small study effects bias was assessed for each meta-analysis based on the regression asymmetry test proposed by Egger and colleagues.38 We considered small study effect bias when the Egger’s test P value<0.10 and the magnitude of association in the largest study (smaller standard error) of a meta-analysis was more conservative than the meta-analysis random effects estimate.39

The excess significance test was used to evaluate whether the expected number of studies (E) differs from the actual observed number of studies (O) with statistically significant results (P<0.05) included in each meta-analysis, regardless of the direction of the association.40 The difference between O and E is evaluated using a two-sided binomial test.40 considering P<0.10 for O greater than E (one-sided P<0.05) as the statistical significance threshold.

All statistical analyses were performed using Stata version 13.0 (College Station, TX).

**Grading the evidence**

As proposed by previous umbrella reviews,26,27,30,31,33 we classified the evidence from meta-analysis with nominally statistically significant results (P<0.05) as strong, highly suggestive, suggestive, or weak, following the criteria described in Table 1,

*Sensitivity analyses*

We performed credibility ceilings sensitivity analyses for associations showing at least weak evidence (P<0.05). Credibility ceilings evaluate potential spurious precision of the combined effect estimates.41 This tool re-estimates the meta-analysis pooled effect size using inflated variances for each study. The variance is inflated by considering the number of studies showing effects on the same direction and the probability of each study for its true effect size to be in different direction from the one suggested by its point estimate.41 We evaluated a series of values to examine what credibility ceiling would be necessary to make the associations non-significant at the 0.05 level.41 Lastly, we performed a sensitivity analyses excluding each criterion used for grading the evidence to analyze the impact in the results.

**RESULTS**

**Description of meta-analyses**

Of the 2,975 records retrieved from the search in databases, we finally selected a total of 19 systematic reviews of observational studies (Figure 1). Systematic reviews of randomized controlled trials were eligible, but were not found in the literature search. Eleven out of 19 reviews (58%) scored ≥ 6 points in the 11-items AMSTAR criteria, indicating a moderate to high methodological quality (Table S4). Limited statistical tests and sensitivity analyses were performed in original meta-analyses. Statistical significance was assessed in all reviews through the fixed/random effect 95% CI (*i.e.*, none reported the exact P value). None of the reviews performed excess significance, credibility ceiling, and 95% prediction intervals tests. I2 heterogeneity estimates (n=17, 90%), small study effect test (n=18, 95%), and number of cases (n=18, 95%) were reported in the majority of the original meta-analyses (Table S1).

Reviews included associations on 22 different cancer sites using 541 original studies, of which 297 (55%) were cohort and 244 (45%) case-control studies. Most of the original studies, 344 (64%), had cancer incidence as outcome, 35 (6%) mortality, and 162 (30%) incidence and mortality. A total of 725,074 cancer cases and 42,428 cancer deaths were included in these meta-analyses. All except for six comparisons (gastric mortality, esophageal mortality, meningioma risk, kidney mortality, Hodgkin lymphoma risk, pancreatic mortality) included more than 1,000 cases in the meta-analyses (Table S5-S6).

Results presented below are based on the primary analysis (‘any physical activity’ and recreational physical activity approaches), which included only cohort studies.

**Summary effect size**

Eight out of the 26 comparisons (31%) based on the any physical activity approach showed statistically significant associations (P<0.05) in the random effect model. From those cancer sites, summary random effect size showed a 0.93 to 0.71 relative risk of cancer among those in the most active category as compared with the least active group. When the random effects P<10-6 was used as a threshold, only overall cancer mortality (RR 0.79; 95% CI 0.75-0.85), colon cancer (RR 0.81; 95% CI 0.75-0.88), and breast cancer incidence (RR 0.87; 95% CI 0.84-0.90) remained statistically significant (Figure 2 and Table S7).

For recreational physical activity, five (25%) out of 20 comparisons showed statistically significant associations based on the P<0.05threshold. Among those, only colon cancer (RR 0.79; 95% CI 0.71-0.86) remained statistically significant at P<10-6 threshold (Figure 3 and Table S8).

**Heterogeneity between studies - I2 and 95% prediction intervals**

Half (n=13) of the meta-analyses of the ‘any physical activity’ approach had I2 smaller than 25%, whereas seven (27%) (all cancer mortality, colon, lung, gastric, bladder, multiple myeloma, and ovary) showed moderate to high heterogeneity (I2 ≥50%). Only all cancer mortality and breast cancer presented a definite direction for the effect size (*i.e.*, the intervals did not include the null value) when 95% prediction intervals were considered (Figure 2 and Table S7).

Regarding recreational physical activity, seven out of 20 meta-analyses (35%) had I2 >50%, and 18 (90%) included null value when 95% prediction intervals presented a definite direction for the effect size (Figure 3 and Table S8).

**Small study effects and excess significance biases**

Out of the 26 studies, four (15%) (breast, all cancer mortality, colon, and pancreas) had a P<0.1 on the Egger asymmetry test and the effect estimate of the largest study was more conservative compared to the summary random effects estimate, indicating potential small-study effect bias. Regarding the excess of significance bias, four (15%) cancer sites (all cancer mortality, colon, lung, gastric) had observed number of studies showing statistically significant results higher beyond chance than the expected (Figure 2 and Table S7).

For recreational physical activity, only multiple myeloma meta-analysis showed small-study effect bias, whereas only lung cancer presented evidence of excess significance bias (Figure 3 and Table S8).

**Robustness of evidence**

None of the associations were supported by strong evidence in the ‘any physical activity’ analyses. The associations between physical activity and breast cancer incidence and all cancer mortality were supported by highly suggestive evidence. Colon cancer, endometrial, and lung cancers were judged as suggestive evidence. Two other cancer sites (meningioma, pancreas, and multiple cancer sites) were supported by weak evidence (Table 1, Figure 2 and Table S7).

There was strong evidence for an association between recreational physical activity and colon cancer (RR 0.79; 95% CI 0.71-0.86). Lung cancer (RR 0.79; 95% CI 0.70-0.90) and all cancer mortality (RR 0.81; 95% CI 0.74-0.90) were supported by a suggestive evidence. Esophageal cancer presented only weak evidence (Table 1, Figure 3 and Table S8).

**Stratified and subgroup analyses**

The stratified analyses results are presented in the appendix (Tables S9-S17). Most of the associations found in the analysis stratified by sex (Table S9-S12) and physical activity domains (total, occupation, and ‘other physical activity’ domains) (Table S13-S15) were graded as weak evidence or were not statistically significant, but data were generally more limited and many studies had not provided separate effects for men and women. Considering case-control studies, the association between any physical activity and colon and breast cancers were supported by highly suggestive evidence (Table S16). For recreational physical activity, only breast cancer was supported by highly suggestive evidence in case-control studies (Table S17).

The majority of the subgroup analyses conducted for each cancer were also supported by weak evidence or were not statistically significant. We found strong evidence for the associations between physical activity and distal colon cancer, breast cancer among women that never used hormone replacement therapy (for estimates based on physical activity measured in hours/week and METs-h/week, adjusted by adiposity), endometrial cancer (*e.g.*, for studies with number of cases higher than 3,500 and with occupational physical activity measures), and non-cardia gastric cancer (Table S18-S39).

**Sensitivity analyses**

Of the eight meta-analyses showing random effects P<0.05 in the ‘any physical activity’ approach, 4 (breast, colon, endometrial, and all cancer mortality) would remain statistically significant even with a 10% credibility ceiling, and two (breast cancer and all cancer mortality) even with a 20% credibility ceiling (Table S7 and Figure S1). Two (colon cancer and all cancer mortality) out of five meta-analyses of recreational physical activity showing random effects P<0.05 remained statistically significant when 10% credibility was used (Table S8 and Figure S2), but none of those survived to 20% credibility ceiling.

 When we performed sensitivity analyses excluding sequentially each criterion used in the grading of evidence, the association between any physical activity and breast cancer, stemming from cohort studies, was supported by strong evidence after excluding the small study effects criterion (Table S40).

**DISCUSSION**

**Principal findings and possible explanations**

In this umbrella review summarizing the evidence of associations between physical activity and different cancer sites, we synthesized data from 22 different cancer sites, 725,074 cancer cases and 42,428 cancer deaths, and evaluated the credibility of the epidemiological evidence. In our primary analysis, stemming from cohort studies, physical activity showed a negative and statistically significant association (P<0.05) with seven cancer sites (colon, breast, endometrial, lung, esophageal, pancreas, and meningioma). However, we found that only the associations with colon cancer and breast cancer were supported by strong evidence and highly suggestive evidence, respectively.

The association between physical activity and incidence of breast and colon cancers was recognized long ago,1,2 whereas associations with other cancer sites has emerged in the last decade.9-17 However, it is also plausible these associations may be flawed due to biases in the literature, overestimating the potential effect of physical activity on the incidence and mortality of cancer. In fact, this phenomenon has been as detected by previous umbrella reviews on other subjects.26,27,30,31,33

Through an array of statistical analyses, we found substantial uncertainty in the literature of physical activity and cancer. When stringent P value was considered (P<10-6), only colon cancer, breast cancer, and all cancer mortality associations remained statistically significant. Moderate to high heterogeneity (I2 ≥50%) was found in a third of the meta-analyses. When such heterogeneity was considered in the 95% prediction intervals, only colon cancer, breast cancer, and all-cancer mortality presented a definite direction for the effect size. We identified few additional hints of bias in the literature though the small study effect and excess significance tests.

**Comparison with other studies**

Criteria for evaluating the evidence have been proposed by different researchers42-45 and organizations.1,2,46 The umbrella review approach evaluates the credibility of evidence using an array of statistical tests and sensitivity analyses to obtain hints of uncertainty and bias in the body of literature. Although is not possible to estimate the exact extent or source of bias that affects the evidence on physical activity and cancer, the criteria that we use aim to capture indirectly the potential effect of biases. The IARC and the WCRF have their own group of experts and criteria to judge the evidence of potential carcinogens to humans, which do not include detailed evaluation of bias in the body of literature. On the other hand, both organizations consider the biological mechanisms evidence, which is beyond the scope of this umbrella review.

Both IARC and WCRF found convincing evidence to support the association between physical activity and colon cancer, in agreement with the conclusions of our umbrella review for recreational physical activity. In the subgroup analysis, we found that only the association with distal colon cancer was supported by strong evidence, whereas proximal colon cancer evidence was judged as suggestive. Colon cancer had suggestive evidence for association with any physical activity with hints of heterogeneity and bias. There are plausible biological mechanisms supporting the association between physical activity and colon cancer, such as reducing body fatness, inflammation, insulin levels and insulin resistance.47

The IARC and WCRF classified the association between physical activity and breast cancer as sufficient (highest grade) and probable (second highest grade), respectively. We found highly suggestive evidence that physical activity decreases the risk of breast cancer, albeit we also observed small-study effect bias for this association. Small-study effect may either be related to bias or random error or heterogeneity.39 Regarding the heterogeneity, the WCRF, but not the IARC, provides separate grading of evidence for menopausal status, suggesting limited evidence for the association between moderate to vigorous physical activity and premenopausal breast cancer and convincing evidence for postmenopausal breast cancer. Similarly, we found that premenopausal and postmenopausal breast cancers were supported by weak and highly suggestive evidence, respectively. Hormone replacement therapy (HRT) is associated with increased risk of breast cancer and may be an important confounder in postmenopausal breast cancer studies.48 We found strong evidence supporting a negative association between physical activity and breast cancer among never HRT users (*i.e.*, analysis less prone to confounding). Additional biological evidence supporting the association between physical activity and breast cancer includes postulated effects on body fatness, certain hormone metabolisms (*e.g.*, fasting insulin, estrogens and androgens) and strengthening of the immune system.48

Our findings are in agreement with IARC and WCRF, except for endometrial cancer, for which the association with physical activity is considered as probable evidence (second highest grade) by the WCRF. We found only suggestive evidence to support the association between any physical activity and endometrial cancer, because the most stringent P threshold (P<10-6) and 95% prediction interval criteria were not satisfied. The P-value criteria might be due to small number of cohort studies on endometrial cancer (n=18) as compared to breast (n=38) and colon cancer (n=28) literature. In fact, when we considered both cohort and case-control designs, and therefore increased the statistical power, the association between physical activity and endometrial cancer was supported by highly suggestive evidence. However, case-control studies presented higher effect size estimates than cohort studies, probably reflecting more bias. The source of heterogeneity (*i.e.*, reflected in the 95% prediction intervals) in our results on endometrial cancer might be due to obesity status. Endometrial cancer is an obesity-related cancer,30 and BMI may mediate the association between physical activity and endometrial cancer.7 For instance, Moore et al. found that leisure-time physical activity (LTPA) was associated with endometrial cancer only among individuals with high BMI.7 Other mechanisms suggested for this association are hormone-related, such as reducing insulin level and insulin resistance, decreasing estradiol and regulating estrogen metabolism.49

Other cancer sites (esophageal, meningioma, lung, pancreas) showed less consistent results with substantial uncertainty in the literature. None of these cancer sites supported more stringent P thresholds used to avoid spurious precision results derived from meta-analyses of observational studies. Three (esophageal, meningioma, pancreas) out of four did not have more than 1000 cases to state conclusion. Heterogeneity (I2 and 95% prediction intervals) and/or bias (small-study effect and excess significant biases) were present in all these meta-analyses. Finally, other cancer sites (bladder, chronic/small lymphocytic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, gastric, glioma, Hodgkin and non-Hodgkin lymphoma, kidney, leukemia, multiple myeloma, ovary, rectum, thyroid) did not showed statistically significant associations at P<0.05threshold. IARC and WCRF also have also considered these associations between physical activity and these cancer sites with limited evidence. However, a recent pooled data from 12 cohorts examined the association between leisure-time physical activity (LTPA) and 26 types of cancer and 187 thousand cancer cases. LTPA was inversely associated (at P<0.05) with 13 cancer sites (colon, breast, endometrial, esophageal adenocarcinoma, liver, kidney, gastric cardia, myeloid leukemia, myeloma, head and neck, rectal, and bladder), and positively associated with melanoma and prostate cancer.7 Although this paper was not included in our umbrella review, as did not meet the eligibility criteria (*i.e.*, was not a systematic review of literature), we recognize its importance to the physical activity and cancer literature. Thus, we applied our grading evidence criteria to their findings. We found that only the association between LTPA and breast, kidney, melanoma, and lung cancers were supported by strong evidence (Table S41). Therefore, despite the uncertainty or bias that was found for many malignancies, these associations could be confirmed as genuine in the future.

Physical activity is associated with obesity and diabetes, and these phenotypes have also been associated to cancer at several sites.26,50,51 Deciphering the exact causal contribution of each of these factors is not easy. Both low within-population variability of and measurement error for physical activity are also important concerns. Future prospective cohort studies with objective measures (*e.g.*, through accelerometers) of physical activity trajectories may reduce misclassification and, therefore, reduce current uncertain evidence for some cancer sites. In parallel, randomized controlled trials of physical activity may help address directly the causal effects. Given the very long follow-up required to study cancer outcomes, these studies are difficult to conduct. However, given its potential major importance, physical activity interventions may need to be studied with large randomized trials, much like other interventions (*e.g.*, drugs) have been studied.52,53

**Limitations**

 Umbrella reviews rely on methodological quality and report transparency of meta-analysis. Despite the fact that the systematic reviews included in our umbrella were of moderate to high methodological quality and were published on average in 2014 (2005 to 2017), some studies may have not been included either because systematic reviews did not identify them or they were too recent to be included.7 We re-performed most of the analysis reported in systematic reviews, however substantial data were missing from some subgroup analyses (Table S42-S46). We encourage future systematic reviews to report each individual-study estimate included in its primary and main subgroup (sex, cancer location, histology) meta-analyses.

Our analyses are based on the comparison between most active and least active groups. A limitation of this approach is that measurement and classification of physical activity across studies are heterogeneous and might not be comparable. Finally, tests used to obtain hints of bias in the body of evidence (small-study effect and excess significance tests) have low power if the meta-analyses include less than ten studies, and they may not identify the exact source of bias.39,54

**CONCLUSIONS**

Despite the fact that physical activity has been associated with a lower risk of several cancers in the literature, the associations for only colon and breast were supported by strong or highly suggestive evidence, respectively. Evidence from other cancer sites was less consistent, presenting hints of uncertainty and/or bias, but could be confirmed as genuine in the future.

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**Table 1: Summary of evidence grading for meta-analyses of cohort studies associating physical activity and risk of developing or dying from cancer.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Evidence** | **Criteria used** | **Decreased Risk** |  |
| **Any** **physical activity** | **Recreational** **physical activity** |  |
| **Strong** | P\*<10-6; >1,000 cases; P<0.05 of the largest study in a meta-analysis; I2<50%; no small study effect¶; prediction interval excludes the null value; no excess significance bias† | None | Colon cancer, inc. or mort. |  |
| **Highly suggestive** | P\*<10-6; >1,000 cases; P<0.05 of the largest study in a meta-analysis | Breast cancer, inc. and All cancer, mort. | None |  |
| **Suggestive** | P\*<10-3; >1,000 cases | Colon cancer, inc. or mort., Lung inc., and Endometrial, inc. | All cancer, mort., and Lung, inc. |  |
| **Weak** | P\*<0.05 | Meningioma, inc. or mort., Multiple cancer sites, inc, or mort., Pancreas, inc. | Esophageal, inc. and Meningioma, inc. or mort. |  |

Abbreviations: inc., incidence; mort., mortality;

\*P indicates the p-values of the meta-analysis random effects model.

¶Small study effect is based on the P-value from the Egger’s regression asymmetry test (P≤0.1) where the random effects summary estimate was larger compared to the point estimate of the largest study (smallest standard error) in a meta-analysis.

†Based on the p-value (P>0.1) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size.

**FIGURE LEGENDS**

**Figure 1: Flow chart of systematic reviews and meta-analyses selection**

**Figure 2:** **Robustness of evidence grading for meta-analyses of cohort studies associating any physical activity and risk of developing or dying from cancer.**

\*Figure 2 Footnote: I, incidence; M, mortality; I+M, incidence and mortality; NS, association not statistically significant (P>0.05); +, yes; -, no; Number of studies refers to number of studies included in the random effect model; Random effect P refers to P*-*value of the summary random effects estimate; Number of cases refers to number of cancer cases or deaths included in the analysis; Largest study with P<0.05 refers to P-value of the largest study (smallest SE) in each meta-analysis; Small study bias is based on the P-value from the Egger’s regression asymmetry test (P<0.1) where the random effects summary estimate was larger compared to the point estimate of the largest study in a meta-analysis; Excess significance bias is based on the p-value (P<0.1) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size; Evidence grading refers to robustness evidence grading criteria;

**Figure 3:** **Robustness of evidence grading for meta-analyses of cohort studies associating recreational physical activity and risk of developing or dying from cancer.**

\*Figure 3 Footnote: I, incidence; M, mortality; I+M, incidence and mortality; NS, association not statistically significant (P>0.05); +, yes; -, no; Number of studies refers to number of studies included in the random effect model; Random effect P refers to P*-*value of the summary random effects estimate; Number of cases refers to number of cancer cases or deaths included in the analysis; Largest study with P<0.05 refers to P-value of the largest study (smallest SE) in each meta-analysis; Small study bias is based on the P-value from the Egger’s regression asymmetry test (P<0.1) where the random effects summary estimate was larger compared to the point estimate of the largest study in a meta-analysis; Excess significance bias is based on the p-value (P<0.1) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size; Evidence grading refers to robustness evidence grading criteria.