Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis

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Background: Epidemiologic studies have reported that cardiorespiratory fitness is inversely associated with mortality from cancer. However, the evidence relating cardiorespiratory fitness to cancer mortality has not yet been quantitatively summarized.

Methods: Following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist, we conducted a systematic review and meta-analysis of the association between cardiorespiratory fitness and total cancer mortality. Relevant studies were identified through a literature search in PubMed up to August 2013 and by screening reference lists of qualifying articles. Data extraction was carried out independently by both authors and summary risk estimates were obtained using random-effects models.

Results: Six prospective studies with an overall number of 71,654 individuals and 2002 cases of total cancer mortality were included. The median follow-up time in the studies was 16.4 years. Cardiorespiratory fitness showed a strong, graded, inverse association with total cancer mortality. Using low cardiorespiratory fitness as the reference group, intermediate and high levels of cardiorespiratory fitness were related to statistically significant decreased summary relative risks (RRs) of total cancer mortality of 0.80 [95% confidence interval (CI) 0.67–0.97] and 0.55 (95% CI 0.47–0.65), respectively. Studies that adjusted for adiposity yielded similar results to those that did not adjust for adiposity.

Conclusion: Increased cardiorespiratory fitness represents a strong predictor of decreased total cancer mortality risk, independent of adiposity.

Key words: cardiorespiratory fitness, cancer mortality, meta-analysis

Introduction
In the past 20 years, interest in the area of energy balance and cancer has been accumulating, and increased energy expenditure has been shown to play an important role in the prevention of cancer incidence and mortality [1]. The terms physical activity and physical fitness are sometimes used interchangeably and the correlation between the two may be perceived as high. However, the correlation between physical activity and cardiorespiratory fitness is only modest, with correlation coefficients ranging from 0.31 to 0.58 [2, 3]. Physical activity is considered any bodily movement produced by the contraction of skeletal muscle that enhances energy expenditure [4]. By comparison, physical fitness does not characterize a behavior but rather, depicts the capacity to achieve a certain performance standard or trait [4, 5].

While the focus in epidemiologic investigations has been on physical activity, little is known regarding the relation of cardiorespiratory fitness to cancer. The sparse data available suggest an apparent beneficial effect of cardiorespiratory fitness on cancer mortality. Specifically, four studies reported a statistically significant reduction in risk of total cancer mortality for high versus low cardiorespiratory fitness in men [6–9]. Two studies reported an inverse association between cardiorespiratory fitness and total cancer mortality in women [8, 10] and in men and women combined [11], but those relations did not reach statistical significance.

To date, no study has quantified the association between cardiorespiratory fitness and risk of total cancer mortality using a meta-analytic approach. We conducted a systematic literature search and meta-analysis to close that research gap.

Materials and methods

Literature search and inclusion criteria
The present systematic review and meta-analysis was conducted following the preferred reporting items for systematic reviews.
and meta-analyses (PRISMA) checklist [12]. We conducted a comprehensive literature search in Pubmed through August 2013 for articles evaluating the association between cardiorespiratory fitness and total cancer mortality using the following search terms: physical fitness OR cardiovascular fitness OR cardiorespiratory fitness OR exercise test AND (neoplasm OR carcinoma OR cancer OR cancer mortality OR mortality). In addition, we searched references from retrieved papers. We included studies that met the following criteria: they (i) were original prospective studies published in English, (ii) investigated the association between cardiorespiratory fitness and total cancer mortality, (iii) measured cardiorespiratory fitness using an exercise test, (iv) reported a risk estimate and 95% confidence intervals (CIs) or sufficient data to calculate them, and (v) took age and smoking as potential confounding factors into account.

**data extraction and quality assessment**

Data extraction was carried out independently by both authors and disagreements were resolved by consensus. The following information was extracted from each article: name of the first author, year of publication, sex, number of participants and cases of cancer mortality, follow-up duration, cardiorespiratory fitness assessment method, covariates adjusted for in the multivariable analysis, and relative risks (RRs) and 95% CIs. When a study provided several adjustment models for potential confounding variables, we extracted the risk estimate of the most fully adjusted model. If a study population was reported on more than once, we included the article with the largest sample size. Studies were excluded if the exposure of interest was combined with another exposure. To judge the quality of the studies, we used the validated Newcastle-Ottawa Scale (NOS) for non-randomised studies [13]. That scale assigns a maximum of nine points to each cohort study (four for quality of selection, two for comparability, and three for quality of outcome and adequacy of follow-up). We defined studies with a NOS of ≥6 as moderate to high-quality studies and studies with a NOS of <6 as low-quality studies.

**statistical analysis**

We combined RRs comparing the highest versus the lowest category of cardiorespiratory fitness in relation to risk of total cancer mortality. In a further analysis, we summarized risk estimates comparing the intermediate versus the lowest category of cardiorespiratory fitness. We defined the intermediate category as the median of all categories. In one study that used four cardiorespiratory fitness categories [7], we used the pooled RR of the second and third categories as the intermediate category. In separate analyses, we calculated the summary RR for cardiorespiratory fitness with and without adjustment for body mass index (BMI) or other measures of adiposity.

We calculated the natural logarithms of the risk estimates $\log(RR)_j$ with their corresponding standard errors $s_{j} = [\log(upper \hspace{1mm} 95\% \hspace{1mm} CI \hspace{1mm} bound \hspace{1mm} of \hspace{1mm} RR) − \log(RR)])/1.96$. A random-effects model was applied to calculate the weighted average of those log RR$s$ while allowing for effect measure heterogeneity. The log (RR)$s$ were weighted by $w_j = 1/(s_{j}^2 + t^2)$ with $s_j$ representing the standard error of log(RR)$j$ and $t^2$ representing the restricted maximum likelihood estimate of the overall variance [14]. We estimated heterogeneity among studies by the $Q$ statistic and the $I^2$ statistic [14]. To examine whether the results could have been influenced by a single study, we conducted a sensitivity analysis by omitting one study at a time. Publication bias was assessed visually and statistically by inspection of funnel plots and by using Egger’s regression test [15] and Begg’s rank correlation test [16]. Data were analyzed using the R-package ‘metafor’ [17]. Two-sided $P$ values were considered statistically significant at an α level <0.05.

**results**

As shown in Figure 1, we identified 6507 articles in PubMed and one article by manual search. After screening titles, we excluded 6357 articles that were unrelated to physical fitness and mortality. In a second round of screening, we reviewed the abstracts of 151 articles, of which we excluded 18 comments, 10 reviews, and 104 articles that were not related to cancer mortality, and four articles that were not related to cardiorespiratory fitness.

Fifteen articles remained and were reviewed in more detail [6–11, 18–26]. We further excluded nine studies due to overlapping study populations [18–26], of which one study additionally did not provide risk estimates [26] and of which three studies investigated site-specific cancer mortality [20–22]. Finally, six articles met the inclusion criteria and were included in the meta-analysis [6–11]. One study provided risk estimates for men and women separately [8] which were both included in the...
meta-analysis because they were considered independent samples. Thus, the present meta-analysis comprised a total of seven risk estimates.

Descriptive data regarding the selected studies are depicted in Table 1. The total number of individuals included was 71,654 with 2002 cases of cancer mortality. All studies were prospective investigations and the duration of follow-up ranged from 7.0 to 24.9 years (median = 16.4 years). In two studies [6, 10], cardiorespiratory fitness was quantified using a maximal treadmill exercise test according to a modified Balke protocol [27]. In one study, cardiorespiratory fitness was assessed by a maximal treadmill-based test [8] according to the Bruce protocol [28]. Two studies conducted cycle ergometer-based cardiorespiratory fitness assessments, of which one study carried out a maximal exercise test [9] and the other a submaximal exercise test [7]. One study used the Canadian Home Fitness Test, a validated submaximal cardiorespiratory fitness test that involves stepping up and downstairs at an age- and sex-specific pace and assesses cardiorespiratory fitness from the immediate postexercise pulse rate [11]. In all studies, risk estimates were adjusted for age and smoking. Most studies additionally adjusted for a wide range of potential risk factors including alcohol consumption, energy intake, chronic illness at baseline, systolic blood pressure, and a measure of adiposity. Risk estimates were adjusted for BMI or another measure of adiposity (waist-to-hip ratio, percentage body fat) in all but one study [11]. Three studies provided risk estimates with and without adjustment for adiposity [6, 8, 10]. All studies had a quality score ≥6 points.

Risk of total cancer mortality was significantly reduced (summary RR = 0.55; 95% CI 0.47–0.65) in individuals with a high cardiorespiratory fitness level compared with those with a lower cardiorespiratory fitness level (Figure 2). No heterogeneity among studies was observed ($I^2 = 0\%$, $P = 0.43$). Removal of individual risk estimates one at a time did not materially alter the summary RR. Egger’s regression test ($P = 0.93$) and Begg’s rank correlation test ($P = 0.54$) indicated no publication bias. Moreover, there was no visual evidence of funnel plot asymmetry. The inverse association between cardiorespiratory fitness and total cancer mortality was very similar in studies with and without adjustment for adiposity (summary RR = 0.55; 95% CI 0.46–0.66) and in studies without adjustment for adiposity (summary RR = 0.58; 95% CI 0.48–0.69; $P$ value for interaction = 0.75) (Figure 3).

The intermediate versus the lowest level of cardiorespiratory fitness was associated with a statistically significant reduced summary RR for total cancer mortality of 0.80 (95% CI 0.67–0.97) (Figure 2). No significant heterogeneity between studies was found ($I^2 = 38\%$, $P = 0.17$). The inverse association between intermediate versus low levels of cardiorespiratory fitness remained evident in studies that did not adjust for adiposity (summary RR = 0.82; 95% CI 0.68–0.99) and also in those that adjusted for adiposity (summary RR = 0.81; 95% CI 0.67–0.98; $P$ for interaction = 0.88).

**discussion**

This meta-analysis identified a significant reduction in risk of total cancer mortality among individuals with high versus low cardiorespiratory fitness (RR = 0.55, 95% CI 0.47–0.65). Risk
reduction was also observed for moderate versus low fitness (RR = 0.80; 95% CI 0.67–0.97). These associations were evident even after adjustment for adiposity, suggesting that cardiorespiratory fitness represents a robust and independent predictor of decreased cancer mortality risk.

To the best of our knowledge, no previous meta-analytic study has quantified the association between cardiorespiratory fitness and risk of total cancer mortality. Investigations directed at evaluating physical activity in relation to cancer mortality have shown variable reductions in risk of cancer mortality, with risk estimates ranging from 0.38 to 0.97 comparing high versus low levels of physical activity [29, 30]. The observed variation in the strength of associations in cancer mortality studies that used physical activity as the exposure may be due to a certain degree of imprecision in assessing physical activity. Although the heritability of maximal oxygen uptake (VO2max) among sedentary adults can reach 50% [31], physical activity habits are considered the main determinant of cardiorespiratory fitness [32].

Because individual cancer types have distinct etiologies, the biologic pathways through which cardiorespiratory fitness influences risk of one type of cancer may differ from the pathogenesis of other cancers. Notwithstanding, the summary RRs of our aggregate end point of total cancer mortality would be expected to represent a weighted average of cancer-specific mortality associations of varying magnitudes. Due to a lack of available data, we were unable to calculate cancer-specific summary RRs. However, data from the Aerobics Center Longitudinal Study revealed that high versus low levels of cardiorespiratory fitness were related to
significant reduced risks of mortality from lung cancer [18], colon cancer [21], colorectal cancer [21], liver cancer [21], and breast cancer [22], suggesting that cardiorespiratory fitness is inversely related to a broad range of cancer outcomes.

Mechanistic studies demonstrate that the beneficial impact of cardiorespiratory fitness involves biological pathways that mediate risk for cancer risk or survival. Potential mechanisms include those that influence insulin sensitivity [33], chronic inflammation [34], steroid hormone levels [35], growth factor production [36], innate immunity [37], antioxidant capacity [38], DNA repair [39], and cell proliferation and apoptosis [40].

To achieve at least a moderate level of cardiorespiratory fitness, a minimum of 150 min per week of moderate intensity aerobic activity or 75 min per week of vigorous intensity aerobic activity is recommended [41]. Because physical activity shows an inverse dose–response relationship with risk of chronic disease and mortality, individuals are likely to achieve additional benefit if they exceed those guidelines.

The primary strength of our study is that it represents the first quantitative meta-analysis on the topic. In addition, it included high-quality prospective studies with long periods of follow-up, adjustment for a wide range of potential confounding variables, and the use of objective and reproducible measures of cardiorespiratory fitness that are not subject to recall bias and are also not likely prone to behavior reactivity and daily variation.

Limitations of our meta-analysis are that the cardiorespiratory fitness categories were based on study-specific cardiorespiratory fitness definitions that varied across studies and could have caused a certain degree of misclassification. Although the included studies controlled for various known risk factors for...
cancer, we cannot rule out the possibility of unknown or residual confounding by dietary, behavioral, social, or genetic factors. For example foods containing dietary fiber, such as vegetables and fruits, may protect against colorectal cancer, and alcohol and foods contaminated with aflatoxins such as cereals and peanuts are a cause of liver cancer [42]. Individuals with high cardiorespiratory fitness in the underlying studies may have shown a healthier eating behavior than those with low cardiorespiratory fitness. Four [7–9, 11] of the six studies [6–11] included in our meta-analysis adjusted for alcohol intake in their analyses, and one study [9] additionally adjusted for intakes of total energy, dietary fiber, and dietary fat. However, we cannot rule out that the observed inverse relation between cardiorespiratory fitness and cancer mortality is confounded by diet.

Confounding by adiposity remains a further concern because individuals with low cardiorespiratory fitness at baseline may have gained more weight during follow-up than those with high cardiorespiratory fitness. However, adjustment for adiposity in the models used in the underlying studies had little impact on the cardiorespiratory fitness and cancer mortality relation, suggesting that regulation of body weight over time explains only a small portion of the benefit of cardiorespiratory fitness.

Caution is also needed in interpreting the strong inverse associations observed because undiagnosed preclinical cancer at study baseline may have caused a decline in cardiorespiratory fitness. In order to minimize the influence that chronic disease may have had on fitness levels at entry, one study represented in our meta-analysis disregarded participants with <1 year of follow-up [10]. Four additional studies in our meta-analysis reduced the potential for reverse causality by conducting secondary analyses in which they excluded individuals with <3 [43], 4 [8], 5 [9], or 6 years [7] of follow-up. The results did not change materially.

Due to lack of data, we were unable to determine whether the magnitude of the association between cardiorespiratory fitness and cancer mortality differed according to particular subgroups defined by age, sex, or ethnicity.

**Conclusion**

In conclusion, findings from our systematic review and meta-analysis of prospective studies revealed that individuals with a high cardiorespiratory fitness level had a 45% reduced risk of total cancer mortality compared with their unfit counterparts. The strong inverse relation of cardiorespiratory fitness to cancer mortality was independent of adiposity level. This suggests that the biologic mechanisms through which cardiorespiratory fitness decreases cancer mortality are not mediated through its association with body weight regulation. Thus, cardiorespiratory fitness plays a potentially important role in protecting against cancer mortality even within the context of weight management programs.

**Disclosure**

The authors have declared no conflicts of interest.

**References**

Concurrent systemic therapy with radiotherapy for the treatment of poor-risk patients with unresectable stage III non-small-cell lung cancer: a review of the literature

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Background: There is no consensus on the therapeutic approach to poor-risk patients with unresectable stage III non-small-cell lung cancer (NSCLC), despite the increasing number of these patients in current clinical practice. In terms of survival, the combination of concurrent systemic therapy with standard radiotherapy might be advantageous over radiotherapy alone. The purpose of this review is to ascertain the feasibility, safety and efficacy of the combination of concurrent systemic therapy and standard radiotherapy in these patients.

Methods: A computer-based literature search was carried out using PubMed and Science Direct for relevant publications; data reported at major conferences in abstract form were also included.

Results: In unresectable stage III NSCLC, advanced age, poor performance status, weight loss and comorbidities are factors that influence treatment options and disease outcomes in clinical practice. Prospective studies including poor-risk...