RESEARCH ARTICLE

Physical Activity and Risk of Lung Cancer: A Meta-Analysis of Prospective Cohort Studies

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Abstract

Background: Previous studies investigating the association of physical activity with risk of lung cancer reported conflicting results. In order to update and improve available evidence on any link, a meta-analysis was performed. Method: We searched the PubMed database for prospective cohort studies investigating the relation of physical activity with risk of lung cancer. The pooled relative risk (RR) with its 95% confidence intervals (95%CI) was used to assess the association. Results: We included 14 prospective studies with a total of 1,644,305 participants, with 14,074 incident lung cancer cases documented during follow-up. Meta-analysis of all 14 studies suggested both high and medium levels of physical activity to be associated with decreased risk of lung cancer compared to the reference group with low level of physical activity (for high level, RR = 0.77, 95%CI 0.73–0.81, P < 0.001; for medium level, RR = 0.87, 95%CI 0.83–0.90, P < 0.001). Subgroup analyses by gender found obvious associations in both men and women. No publication bias was observed. Conclusion: Our findings suggest that high and medium levels of physical activity have a beneficial effect on lung cancer by reducing the overall risk of tumour development among both men and women.

Keywords: Physical activity - lung cancer - meta-analysis - protective effect

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Introduction

Lung cancer is one of the leading causes of cancer deaths in the world, and is a major contributor to the world's burden of disease (Herbst et al., 2008; Goldstraw et al., 2011). Distinct measures of primary prevention have been investigated, and there are convincing evidence for respective risk reductions of morbidity and mortality caused by lung cancer by primary prevention (Herbst et al., 2008; Ito et al., 2011). Increased physical activity has been associated with a reduction in the incidence and mortality from all-site cancer and some site-specific cancers in samples of primarily nonsmoking individuals; however, little is known about whether physical activity is associated with similar risk reduction of lung cancer (Thune and Furberg, 2001). There is some evidence of an association between physical activity and lung cancer etiology. Several studies suggest that physical activity is associated with decreased risk of lung cancer in men and women, and both leisure time and occupational physical activity are generally considered to provide protective effects on health (Sinner et al., 2006; Yun et al., 2008; Leitzmann et al., 2009). However, other studies didn't found physical activity to be protective against lung cancer in both men and women (Colbert et al., 2002; Steindorf et al., 2006). In view of these inconsistencies a systematic review and meta-analysis of the current state of knowledge seems warranted. We therefore performed this systematic review with an exclusive focus on findings from prospective cohort studies of physical activity and risk of lung cancer. We attempted to follow the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines to report the present meta-analysis (Stroup et al., 2000).

Materials and Methods

Search Strategy

We conducted a comprehensive search in the Pubmed database from its inception through May 19, 2012. The following search terms were used: 1) physical activity or exercise; 2) lung cancer, or lung carcinoma; and 3) cohort study, cohort studies, prospective study, or prospective studies. There was no language limitation. All references cited in those included studies were also reviewed to identify additional published articles not indexed in the common database.

Study Eligibility

Studies were considered eligible if they met the following criteria: 1) Prospective cohort studies; 2) Exposure of interest was medium or high level of physical

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activity; 3) The outcome of interest was lung cancer; 4) Peer-reviewed English articles with original data; 5) Healthy populations without history of disease of interest; 6) Sample size: ≥1,000; 7) Follow-up: ≥5 years; 8) Adjustment for relevant confounding factors; and 9) Estimation of relative risk (RR), or hazard ratio (HR), with 95% confidence interval (CI) (or data to calculate them) were reported. Overlapping study or studies containing overlapping participants were all excluded. In case of multiple publications from the same institution with identical or overlapping patient cohorts, the most informative report was included.

Data Extraction and Quality Assessment

Two investigators independently extracted data, and disagreements were resolved through consensus. Data retrieved from the articles included the following: author, year of publication, study design, study population, participant characteristics, measurement of exposure and outcome variables, adjustment for potential confounding, and estimates of associations. We distinguished three levels of physical activity: high, medium, and low. The lowest category was defined as low level physical activity (reference group), the highest category as high level physical activity. All categories in between were pooled to represent a medium level physical activity. For each selected study we extracted a RR or HR for the high versus the low physical activity group, and for the medium versus the low physical activity group, respectively. Quality assessment for cohort studies in this meta-analysis was assessed using the Newcastle Ottawa scale (NOS) as recommended by the Cochrane Non-Randomized Studies Methods Working Group (Wells et al., 2000; Millett et al., 2008). Given the variability in quality of observational studies found on our initial literature search, we considered studies that met 5 or more of the NOS criteria as high quality.

Statistical Analysis

We calculated the pooled RR with its corresponding 95%CI to assess the association of physical activity with risk of lung cancer, and an RR less than 1 indicated a beneficial effect on lung cancer in participants with high and medium level of physical activity. The significance of the pooled RR was determined by the Z test and a P value of less than 0.05 was considered significant. Data for were analyzed with all men and women in a first step and then men and women were analyzed separately. In our study, two models of meta-analysis for dichotomous outcomes were conducted: the random-effects model and the fixed-effects model (Mantel and Haenszel, 1959, DerSimonian and Laird, 1986). To assess the between-study heterogeneity, the I^2 statistic to quantify the proportion of the total variation due to heterogeneity was calculated (Higgins et al., 2003). The I^2 index expressing the percentage of the total variation across studies due to heterogeneity was calculated to assess the between-study heterogeneity. I^2 values of 25%, 50%, and 75% were used as evidence of low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). If high heterogeneity existed, the random-effects model was used to pool the results; otherwise, the fixed-effects model was used to pool the results when I^2 value was less than 50%. To validate the credibility of outcomes in this meta-analysis, sensitivity analysis was performed by sequential omission of individual studies or by omitting studies without high quality (Tobias, 1999). To detect publication biases we explored heterogeneity in funnel plots using Begg's asymmetry method. In addition, we also performed Egger linear regression test at the $P < 0.10$ level of significance to assess the funnel-plot's asymmetry (Egger et al., 1997). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas). A P value < 0.05 was considered statistically significant, except where otherwise specified.

Results

Study Characteristics

The systematic search identified 280 potentially relevant articles according to the inclusion criteria. Of these, 22 articles were preliminary included and assessed further for eligibility. After data extraction and quality assessment, 8 articles were excluded for non-relevant or no data available. Thus, 14 prospective studies with a total of 1,644,305 participants were finally included into this meta-analysis (Albanes et al., 1989; Severson et al., 1989; Sellers et al., 1991; Lee and Paffenbarger, 1994; Steenland et al., 1995; Thune and Lund, 1997; Lee et al., 1999; Wannamethee et al., 2001; Colbert et al., 2002; Sinner et al., 2006; Steindorf et al., 2006; Sprague et al., 2008; Yun et al., 2008; Leitzmann et al., 2009). The follow-up arranged from 6 years to 18 years, while the sample size arranged from 4,832 participants to 501,148 participants. There were 5 studies performed in both men and women, 7 performed in men, and 2 performed women. There were a total of 14,074 incident lung cancer cases documented during follow-up. Adjustment for potential

Table 1. Summary of Meta-analysis on Physical Activity and Lung Cancer Risk

	Studies	RR(95%CI) #	P value	Pooled model	I^2
Medium level physical activity versus low level physical activity					
Total participants	12	0.87(0.83-0.90)	<0.001	Fixed effects	7.20%
Men	10	0.87(0.83-0.91)	<0.001	Fixed effects	37.60%
Women	6	0.89(0.82-0.97)	0.006	Fixed effects	0.00%
High level physical activity versus low level physical activity					
Total participants	13	0.77(0.73-0.81)	<0.001	Fixed effects	10.80%
Men	11	0.78(0.73-0.83)	<0.001	Fixed effects	31.30%
Women	7	0.76(0.69-0.84)	<0.001	Fixed effects	0.00%

(# RR (95%CI), relative risk with 95% confidence interval)

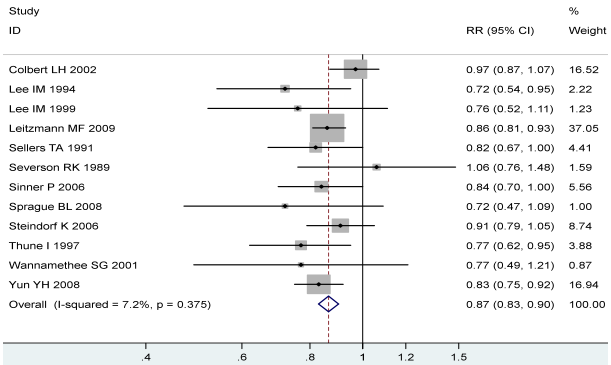

Figure 1. Meta-analysis of the Association Between Mmedium Level Physical Activity and Risk of Lung Cancer

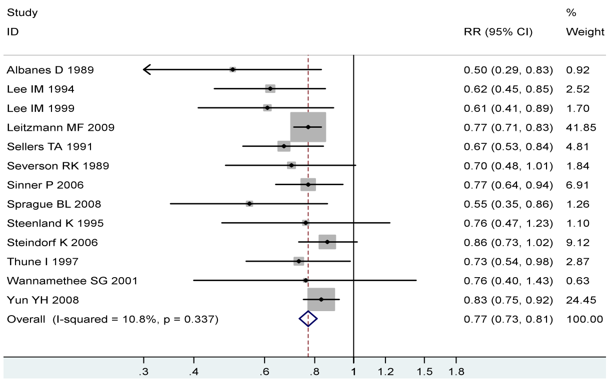

Figure 2. Meta-analysis of the Association Between High Level Physical Activity and Risk of Lung Cancer

confounding was performed in all included studies, and age, body mass index and smoking were main potential confounding factors used in the adjustment.

Meta-analysis

Figure 1 demonstrated the association between medium level of physical activity and risk of lung cancer. There was no obvious heterogeneity between those 12 studies ($I^2 = 7.2\%$), and we used fixed effects model to pool the RRs. Meta-analysis showed medium level of physical activity was associated with decreased risk of lung cancer compared to the reference group with low level of physical activity (fixed effects RR = 0.87, 95%CI 0.83–0.90, P < 0.001) (Figure 1, Table 1). Among men, the pooled RR of in the group with the medium level of physical activity was 0.87 (95% CI 0.83–0.91, P < 0.001) compared to the reference group with low level of physical activity (Table 1). Among women, the pooled RR of in the group with the medium level of physical activity was 0.89 (95% CI 0.82–0.97, P = 0.006) compared to the reference group with low level of physical activity (Table 1).

Figure 2 demonstrated the association between high level of physical activity and risk of lung cancer. There was no obvious heterogeneity between those 13 studies (I2 = 10.8%), and we used fixed effects model to pool the RRs. Meta-analysis showed high level of physical activity was associated with decreased risk of lung cancer compared to the reference group with low level of physical activity (fixed effects RR = 0.77, 95%CI 0.73-0.81, P < 0.001) (Figure 2, Table 1). Among men, the pooled RR of in the group with the high level of physical activity was 0.78 (95% CI 0.73–0.83, P < 0.001) compared to the reference group with low level of physical activity (Table 1). Among women, the pooled RR of in the group with the high level of physical activity was 0.76 (95% CI 0.69–0.84, P < 0.001) compared to the reference group with low level of physical activity (Table 1).

Publication Bias

Funnel plot and Egger's test were performed to assess the publication bias in this meta-analysis. Funnel plots' shape of all analyses did not reveal obvious evidence of asymmetry, and all the P values of Egger's tests were more than 0.05, providing statistical evidence of funnel plots' symmetry. Thus, the results above suggested that publication bias was not evident in this meta-analysis.

Discussion

Previous studies investigating the association of physical activity with risk of lung cancer reported conflicting results. In order to update and improve available evidence on the association above, a meta-analysis was performed. We included 14 prospective studies with a total of 1,644,305 participants, with 14,074 incident lung cancer cases documented during follow-up. Meta-analysis of total 14 studies suggested both high and medium level of physical activity were associated with decreased risk of lung cancer compared to the reference group with low level of physical activity (For high level, RR = 0.77, 95%CI 0.73–0.81, P < 0.001; For medium level, RR = 0.87, 95%CI 0.83–0.90, P < 0.001). Subgroup analyses by gender found obvious associations above both in men and women. These effects were independent of the impact of major lung cancer risk factors which were considered as confounders. Our findings suggest that high and medium level of physical activity has a beneficial effect on lung cancer by reducing the overall risk of incident lung cancer among both men and women.

In epidemiological research the prospective observational study is considered a gold standard approach because of its temporal sequence, sample size, statistical power calculation, and the quantification of subsequent disease risk following exposure and allowing for adjustment for confounding variables in multivariate analysis. Prospective cohort studies are expensive and time-consuming, but due to their methodological strengths their findings provide a strong case of credibility, in particular if supported by results from intervention studies demonstrating cancer risk reduction as a function of increased physical activity (Thune and Furberg, 2001). Physical activity might influence the risks for cancers at several sites, and the evidence is most consistent for colon cancer, pancreatic cancer, endometrial cancer and prostate cancer (Wolin et al., 2009; Moore et al., 2010; O'Rorke et al., 2010; Liu et al., 2011). However, the influence of physical activity on lung cancer is still unclear. Our meta-analysis suggests high and medium level of physical activity has a beneficial effect on lung cancer by reducing the overall risk of incident lung cancer among both men and women, which provide new evidence for the preventive effect on cancer of physical activity.

Besides, there is also evidence for that physical activity has positive effects on physiology, body composition, physical functions, psychological outcomes, and quality of life in patients after treatment for various cancers (Fong et al., 2012). Thus, there are obvious direct implications for both the prevention and treatment of lung cancer by increasing the physical activity.

The development of lung cancer might be affected through various mechanisms (Goldstraw et al., 2011; Missaoui et al., 2011). Physical activity may decrease the risk of lung cancer by several possible ways. For example, physical activity might enhance immune function and reduce the concentrations of carcinogenic agents in the airways. Increased pulmonary function and perfusion reduce the interaction time with the carcinogenic agents in the airways, although exposure to air pollutants might also increase with increased respiration. Another possibility is that higher levels of physical activity are associated with decreased insulin-like growth factor levels and increased insulinlike growth factor binding protein and thus inhibit cellular mitosis. These mechanisms could operate separately or in combination and modify the risk for lung cancer among physically active individuals. In addition, there are protective effects resulting from body weight control and its effect on high blood pressure and decreased risk of metabolic syndrome caused by physical activity.

Several potential limitations have to be addressed. Firstly, this meta-analysis evaluated physical activity and risk of lung cancer as an overall category, without distinguishing between occupational physical activity and leisure time physical activity. Previous studies suggest there might be different effects on cancer risk between occupational physical activity and leisure time physical activity, and it would be very interesting to know the exact effect (Moore et al., 2010, Liu et al., 2011). Further studies may investigate the possible different effects on cancer risk between occupational physical activity and leisure time physical activity on risk of lung cancer. Secondly, it is difficult to elucidate the specific role of physical activity as part of a health-related lifestyle that produces favorable effects on diet, body weight control and reduction or lack of addictive behaviors, such as cigarette smoking. Though adjusting for these factors in multivariate statistical analysis has been performed in many of the reported studies, this approach may not do justice to the complex web of causation produced by comprehensive health-related lifestyles. Finally, there was no accurate assessment of physical activity and there was no uniform measurement in those 14 studies included. Assessments varied quite substantially with regard to frequency, intensity and duration of physical activity. Thus, there might be risk of inaccurate assessment in the present meta-analysis.

In conclusion, our findings suggest that high and medium level of physical activity have a beneficial effect on lung cancer by reducing the overall risk of incident lung cancer among both men and women. The findings have obvious direct implications for primary and secondary prevention of lung cancer.

Acknowledgements

The author(s) declare that they have no competing interests.

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