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Review

Physical activity and the risk of developing lung cancer among smokers: A meta-analysis

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ABSTRACT

Objective: To investigate the relationship between physical activity and lung cancer among smokers and whether this relationship differed according to physical activity intensity, smoking status, and gender.
Design: Meta-analysis.
Methods: A computerized bibliographical search was conducted in five databases. Study inclusion criteria were: (i) the study population was not diagnosed with lung cancer at baseline; (ii) the study provided information concerning the effect size of physical activity on the risk of developing lung cancer in smokers; and (iii) the study distinguished different physical activity intensity levels. Two authors independently extracted data and assessed the methodological quality. Pooled rate ratios (RR) were calculated for all data, and for subgroups of physical activity intensity, smoking status, and gender.
Results: Pooled RRs of 7 cohort studies showed that physical activity was associated with a reduced risk of lung cancer in smokers (RR = 0.82, 95% CI = 0.77; 0.87). We did not find clear dose–response relationship regarding exercise or smoking intensity, i.e. high levels of physical activity did not show a higher risk reduction than moderate physical activity levels, and the association between physical activity and risk reduction did not differ between heavy and light smokers. The reduced risk associated with physical activity was greater in women than in men ($p = 0.03$), but this finding was based on only one study that reported data on women.
Conclusions: Results of this meta-analysis indicate that leisure time physical activity is associated with reduced risk of developing lung cancer among smokers. Future studies should provide insight into a potential dose–response relationship, and should use reliable and valid physical activity measurements.

1. Introduction

Worldwide, lung cancer is the most commonly diagnosed cancer, accounting for 14% of new cancer cases.[1] Lung cancer has, in general, low survival rates and is the most common cause of cancer death, with 29% of the total cancer deaths in men and 26% in women.[1] These facts emphasize the importance of lung cancer prevention and knowledge of modifiable risk factors. Smoking is the leading cause of lung cancer,[2] and it is an important risk factor for cardio- and cerebrovascular disease as well.[3] Smoking is a major public health concern.[4,5] Smokers are 14 times more likely to develop lung cancer than non-smokers.[6] However, not everybody who smokes develops lung cancer, suggesting individual variation in susceptibility to smoke-associated respiratory carcinogens.[7] Beside interventions focusing on smoking cessation, there are also strategies that may reduce the smoking-induced tobacco harm. Physical activity (PA) may be an important potential modifiable factor influencing lung cancer risk and incidence.[8] In general, both male and female smokers tend to get less PA than non-smokers.[9,10] The proportion of heavy smokers with a low PA level has been reported to be 20% higher than in non-smokers.[9]

The mechanisms by which PA might reduce the risk of developing lung cancer in smokers are not yet fully understood. Several mechanisms have been hypothesized, including increased pulmonary function reducing concentrations of carcinogenic agents in the lungs and shorter duration of agent–airway interaction, enhanced immune function, reduced inflammation, enhanced DNA repair capacity, changes in growth factor levels, and possible gene–physical activity interactions.[7,11–14] PA may also reduce potential smoking-induced oxidative stress in lung tissue.[15,16]

Two reviews[7,17] and one meta-analysis[18] indicated that regular participation in PA has the potential to prevent the development of lung cancer in the general population. Observational epidemiological studies showed that total and recreational PA reduces the risk

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of lung cancer by 20–30% for women and 20–50% for men, and that there is evidence of a dose–response effect.[7] However, these previous studies also included non-smoking populations, and therefore do not provide evidence for a protective effect of PA among smokers.

Health risk behaviors often tend to cluster.[19] Therefore, in addition to their independent effect on lung cancer development, smoking and PA may also have an interaction effect.[20] Consequently, findings from previous reviews may not be generalizable to the smoking population.

Therefore, we conducted a systematic review and meta-analyses to investigate the relationship between PA and lung cancer in smokers. In addition, we studied differences in this relationship according to PA level, smoking status, and gender.

2. Methods

This meta-analysis was conducted taking into account the checklist proposed by Stroup et al.[21] A computerized literature search was conducted in the following electronic databases up to November 2011: PubMed, EMBASE, CINAHL, SPORTDiscus, and CENTRAL (the Cochrane Central Register of Controlled Trials). Each database was searched since its start date. Two authors (EvL and IV) independently searched the databases. The search strategy was built upon (i) population type (smokers); (ii) lifestyle factor (e.g. physical activity, sports), (iii) outcome (lung cancer), (iv) and research design ('prospective', 'retrospective cohort study', or 'case–control study'), and keywords (e.g. MESH-headings, EMTREE) and free text words including "smoking", "physical activity", "exercise", "sports" and "lung neoplasms" were used. The complete search strategy of the literature search is available upon request. The search was restricted to papers in the English, Dutch or German language. The reference lists of all selected papers and published reviews on PA and lung cancer were screened for additional relevant papers.

The studies had to meet the following inclusion criteria: (1) the design was a cohort study including a population that was not diagnosed with lung cancer at baseline or a case control study; (2) the study included assessments of leisure time PA; (3) the study provided information concerning the effect sizes of PA on and lung cancer risk in smokers; and (4) the study compared at least two different PA levels, e.g. more physically active subjects versus least physically active subjects (i.e. reference category).

Two authors (EvL and IV) independently screened titles and abstracts, and if necessary full texts, to determine whether the paper met the inclusion criteria. The papers of which the authors' opinion was initially different were discussed until consensus was reached.

Two authors (LB and AS) independently rated the methodological quality of the studies, using a methodological scoring list, which was based on a methodological scoring list of Wolin et al.[22] One point was assigned to studies that used objective measures to assess PA or standardized questionnaires (self-report or interview) of which information regarding reliability and validity was available in literature, and one point for quantification of PA (i.e. 0.5 points for PA intensity and 0.5 points for PA frequency). Studies that used medical records to evaluate the outcome received two points, whereas those that used a death certificate or tumour registry received one point. A maximum of one point was assigned for the assessment of smoking status. Studies that included pack-years of smoking received one point. When the number of cigarettes per day or the number of smoking years was mentioned, 0.5 points were given for each. A maximum of two points was assigned for the assessment of confounding. Studies that adequately adjusted for sociodemographic factors (i.e. three out of the following four: age, employment/education/income; partner/marital status, and ethnicity) received 0.5 points. Studies that adjusted for body mass index received 0.5 points, for lifestyle (diet and alcohol) 0.5 points, and family history 0.5 points. Cohort studies with a response rate over 80% received one point. case–control studies with a response rate over 80% for cases received 0.5 points, whereas those with a response rate of over 80% for controls received 0.5 points, for a total of 1 point. Consequently, the maximum quality score was eight for both cohort and case–control studies. A methodological score <50% of the maximum score (i.e. >4 points) was considered as low quality,[23] and a score ≥50% was considered adequate.

Two authors (EvL and IV) independently extracted data from the selected studies regarding (i) study design, (ii) sample size, (iii) population, (iv) follow-up duration, (v) level and definition of physical activity, (vi) smoking status, and (vii) the main findings.

Adjusted rate ratios (including 95% confidence intervals [CI]) were extracted from each cohort study for pooling in Comprehensive Meta-Analysis (CMA; version 2.2.046). First, we calculated the overall effect of PA (according to operationalizations used by authors) on lung cancer in which the lowest level of PA was used as the reference category. As we expected considerable heterogeneity, we calculated pooled rate ratios with the random effects model. This model assumes that the included studies are drawn from 'populations' of studies that differ from each other systematically (heterogeneity). In this model, the prevalence resulting from the included studies not only differ because of the random error within studies (fixed effects model), but also because of true variation in prevalence from one study to the next. We first tested the heterogeneity under the fixed model using the statistics I^2 and Q. I^2 describes the variance between studies as a proportion of the total variance. A value of 0% indicates no observed heterogeneity, and a larger value shows increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity.[24] When P values of the Q are above 0.05, the total variance is due to variance within studies and not to variance between studies.

In addition, we conducted subgroup analyses to evaluate differences in effects with respect to PA level (moderate, moderate–high and high levels of PA compared with the lowest PA level, i.e. reference category), smoking status (heavy vs. light smoker, with cut-points between 15 and 20 cig/day), and gender (male and female). A mixed effect analysis was used, in which a random effects model was used to combine studies within each subgroup. A fixed effect model was used to combine subgroups and yield the overall effects. The study-to-study variance was not assumed to be the same for all subgroups. The overall statistics was computed by combining data across different categories of PA, smoking status, and gender, treating these as independent subgroups (i.e. cohorts).

3. Results

The literature search yielded 534 records, which were screened by titles and abstracts. We excluded 514 records that were out of scope. Full text articles of the 20 potentially relevant articles were assessed for eligibility. After reading full text, we excluded four references that did not focus on smokers that were free of lung cancer at baseline (inclusion criterion 1), and eight references in which effect sizes of PA on the risk of developing lung cancer in smokers were not reported (inclusion criterion 2). Consequently, seven cohort studies[11,14,25–29] and one case–control study[30] met the inclusion criteria. Two[11,14] of these eight studies were conducted before 2002.

The methodological quality score of the cohort studies papers ranged from 31 to 63% and it was 56% for the case–control study,[30] see Table 1. Two[14,29] out of seven cohort studies (29%) were of low quality. All studies used self-reported questionnaires to assess PA. Only one study[11] reported information on validity and reliability of