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Physical activity and risk of lung cancer

I-M Lee,[a,b] HD Sesso[a,b] and RS Paffenbarger Jr[a,c]

Background Physical activity has been proposed to decrease lung cancer risk; however, few data are available. Further, no studies have examined specific kinds and intensities of activities.

Methods We conducted a prospective cohort study among 13 905 male Harvard University alumni (mean age, 58.3 years), free of cancer. Men reported their walking, stair climbing and participation in sports or recreation on baseline questionnaires in 1977, and the occurrence of lung cancer on follow-up questionnaires in 1988 and 1993. Death certificates were obtained for decedents through 1992 to determine lung cancers not previously reported.

Results During follow-up, 245 men developed lung cancer. Adjusting for age, cigarette smoking, and body mass index, the relative risks of lung cancer associated with <4200, 4200–8399, 8400–12 599 and ⩾12 600 kJ/week of estimated energy expenditure at baseline were 1.00 (referent), 0.87 (95% CI : 0.64–1.18), 0.76 (95% CI : 0.52–1.11), and 0.61 (95% CI : 0.41–0.89), respectively; *P* trend = 0.0008. Similar trends were observed among non-smokers or former smokers in 1977 (82.7% of men) as well as among those who smoked >20 cigarettes a day in 1977 (8.0%), although the findings in the latter group were not statistically significant, possibly due to the small number. Walking, climbing stairs and participating in activities of at least moderate intensity (⩾4.5 MET, or multiples of resting metabolic rate) were each inversely associated with lung cancer risk, independent of the other activity components. However, light intensity activities (<4.5 MET) did not predict lung cancer risk.

Conclusions These data indicate that physical activity may be associated with lower risk of lung cancer among men. An energy expenditure of 12 600 kJ/week, achievable by perhaps 6–8 hours of at least moderate intensity physical activity, may significantly lower risk. Further studies are required to confirm these observations.

Keywords Cigarette smoking, lung cancer, physical activity

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Lung cancer mortality rates have increased dramatically in the US since the beginning of the twentieth century.[1] However, in recent years, the upward trend has begun to slow down, or even reversed, in younger individuals among whom cigarette smoking is less prevalent.[2] Nonetheless, lung cancer is still an important cause of morbidity and mortality today. An estimated 171 500 people in the US will be newly diagnosed with this disease in 1998, while almost as many will die from the disease.[1] While some 80–90% of lung cancers in the US appear to be caused by cigarette smoking,[3] many individuals who smoke never develop this disease. Occupational exposures, urban air pollution, genetic factors, and lifestyle habits may also play a role in the aetiology of lung cancer. A recent study from Norway reported an inverse association between physical activity and lung cancer risk.[4] Investigators hypothesized that the increased pulmonary ventilation and perfusion that occurs with physical activity may lead to reduced interaction time and concentration of carcinogens in the airways and, hence, reduced rates of lung cancer. However, other mechanisms, such as enhanced immune function with increased physical activity, also may explain the association.

Few data are available regarding the association of physical activity with lung cancer risk. Previously, we had examined this question in men whose physical activity habits were initially assessed in 1962 or 1966, and who were followed through 1988 for the onset of lung cancer.[5] As with the Norwegian study, we observed an inverse association between physical activity and lung cancer incidence rates. In the present study, we sought to

[a] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.

[b] Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

[c] Division of Epidemiology, Stanford University School of Medicine, Stanford, CA, USA.

investigate whether our previous findings would persist when following these men over a later time period. In addition, because of recent interest in the kinds of physical activity that are optimal for health,[6] we further examined different components of physical activity in relation to lung cancer risk.

Methods

Study subjects

The Harvard Alumni Health Study is an ongoing study of the predictors of chronic diseases among men entering Harvard University as undergraduates between 1916 and 1950. We first mailed a health questionnaire to surviving alumni in either 1962 or 1966. After this initial survey, we periodically resurveyed all surviving alumni in the relevant classes to obtain updated information on health habits and medical history.

For the present study, potentially eligible subjects were 17 835 alumni who returned a health questionnaire in 1977. We then excluded men who reported a history of cancer on the questionnaire (n = 1339) and those not providing information on physical activity and other variables used in analyses (n = 452). Of the remaining 16 044 men, we successfully followed 13 905 (i.e. they subsequently returned another questionnaire or were known to have died by 1992; details provided below), or 87%. These 13 905 represent the subjects used in the present analyses.

Assessment of physical activity and other predictors of lung cancer

We asked alumni on the 1977 questionnaire to estimate the number of blocks walked daily, the number of flights of stairs climbed daily, and to list all sports or recreation in which they had actively participated during the past year.[7] For each sport or recreation listed, we asked about frequency (weeks per year) and duration (time per week when active). This assessment of physical activity has been shown to be reliable and valid in large population studies for ranking individuals according to their physical activity.[8–10] For example, the test-retest correlation coefficient over one month for energy expenditure was 0.72, while questionnaire estimates of energy expenditure compared with estimates from physical activity records yielded a correlation coefficient of 0.65.[10]

Using the information provided, we estimated total energy expended per week in physical activity. Walking one block daily rated 235 kJ/week; climbing one flight of stairs daily required 118 kJ/week. To each sport or recreation, we assigned a multiple of resting metabolic rate (MET score).[11] Since resting metabolic rate is approximately 4.2 kJ/kg body weight/hour, we estimated the average weekly energy expenditure for that activity by multiplying its MET score by 4.2, body weight, and hours per year of participation, then dividing by 52. We summed kilojoules per week from walking, stair climbing, and sports or recreation to estimate total energy expenditure. We then defined four categories: $<$4200 (32.2% of men), 4200–8399 (28.4%), 8400–12 599 (18.1%) and $\geq$12 600 kJ/week (21.4%).

We additionally were interested in the association of the different components of physical activity with lung cancer risk. Therefore, we examined separately walking, stair climbing, and sports or recreation. We categorized men into approximate fourths of distance walked (one block = 0.13 km): $<$5 (31.7% of men), 5 to $<$10 (21.7%), 10 to $<$20 (26.1%) and $\geq$20 km/week (20.5%). Similarly, we grouped men into approximate fourths of flights climbed (two flights = one storey): $<$10 (23.9% of men), 10 to $<$20 (21.0%), 20 to $<$35 (20.7%) and $\geq$35 storeys/week (34.3%). For sports or recreational activities, we calculated, separately, energy expenditure from light ($<$4.5 MET) and at least moderate intensity ($\geq$4.5 MET) activities. (Examples of the latter activities reported by alumni include dancing, bicycling, jogging or running, digging or filling in garden, and shovelling snow.) For light energy expenditure, we defined five groups: none (64.4% of men), 1 to $<$1050 (9.8%), 1050 to $<$2520 (8.0%), 2520 to $<$5880 (8.7%), and $\geq$5880 kJ/week (9.1%). For energy expended on activities of at least moderate intensity, we did likewise (38.2%, 15.6%, 12.4%, 16.2% and 17.6%, respectively). These cutpoints were chosen so that among those who did report some sport or recreation, men would be approximately evenly distributed among the remaining four categories of energy expenditure. Further, the choice of identical cutpoints would enable direct comparison of incidence rates between, for example, men who expended 1050 to $<$2520 kJ/week in light activities and those who expended the same amount of energy, but in at least moderately intense activities.

On the 1977 questionnaire, we also asked about cigarette smoking, weight and height. On this questionnaire, men were asked whether they currently smoked and, if so, the number of cigarettes smoked daily. Since this information was limited, we obtained additional information from a previous questionnaire, mailed in either 1962 or 1966 (hereafter referred to as 1962/1966), where we had ascertained whether men had never smoked, had previously smoked, or were currently smoking (available on a subset of 11 849 men). The ages of starting and stopping smoking also were asked. In order to update information on smoking status during follow-up, we made use of information from another questionnaire mailed in 1988, where we asked about cigarette smoking habit (never, past, or current smoker), the number of cigarettes smoked daily, and the ages of starting and stopping smoking.

Ascertainment of lung cancer

In 1988 and again in 1993, we sent health questionnaires to surviving alumni. In each survey we inquired whether a physician had ever diagnosed cancer and, if so, the site and year of first diagnosis. Self-reports of physician-diagnosed, site-specific cancers among alumni are believed to be valid.[12,13] We used death certificates to ascertain additional lung cancers (underlying or contributing cause of death) not reported in the 1988 or 1993 health surveys. Deaths occurring through 1992 were traced using information from the alumni office to obtain death certificates. Mortality follow-up in this cohort is virtually complete.[14]

Statistical analyses

We used proportional hazards regression to analyse time to the occurrence of lung cancer or censoring (death or latest questionnaire return).[15] We tested proportionality assumptions and found no evidence of violation. We modelled hazard ratios (relative risks, RR) of lung cancer as a function of total energy expenditure (using the categories described above), adjusting for age (in years), cigarette smoking, and body mass index (categorized into approximate fifths: $<$22.5, 22.5 to $<$23.5, 23.5 to $<$24.5, 24.5 to $<$26.0, or $\geq$26.0 kg/m^2). In our main analyses, we categorized men according to their smoking habit

Table 1 Baseline characteristics of Harvard alumni according to physical activity, 1977

	Physical activity,[a] kJ/week			
Characteristic	<4200 (n = 4476)	4200–8399 (n = 3946)	8400–12 599 (n = 2513)	⩾12 600 (n = 2970)
Mean age, years (SD)	60.2 (9.5)	57.8 (8.9)	56.8 (8.6)	57.3 (8.7)
Mean energy expenditure,[a] kJ/week	544	1466	2446	4831
Cigarette habit (%)				
Non-smoker	79.8	83.4	83.0	85.8
Current smoker of:				
⩽20 cigarettes/day	9.7	7.6	8.7	7.5
>20 cigarettes/day	9.6	7.9	7.5	6.0
unknown amount	0.9	1.1	0.8	0.7
Body mass index, kg/m^2 (%)				
<22.5	23.4	22.9	22.4	22.0
22.5 to <23.5	14.0	14.8	15.2	15.7
23.5 to <24.5	17.0	20.1	20.5	19.3
24.5 to <26.0	19.2	20.4	21.1	20.7
⩾26.0	26.5	21.9	20.9	22.3

[a] Estimated from walking, climbing stairs and participating in sports or recreational activities.

assessed in 1977 (non-smoker, current smoker of ⩽20 cigarettes per day, >20 cigarettes per day, or unknown amount). Since this may not have adequately controlled for cigarette smoking, we also conducted two additional analyses. First, we made use of information obtained on the 1962/1966 questionnaire, as well as the 1977 questionnaire, to adjust for smoking status (never, past, or current smoker), number of cigarettes smoked daily, and duration of smoking in years, all ascertained as of 1977. Second, we adjusted for smoking status, number of cigarettes smoked daily, and duration of smoking in years, all ascertained as of 1977, and updated these variables as of 1988. We calculated 95% CI for estimated RR and used two-tailed tests of significance. Tests for trend were assessed by treating the different physical activity categories as a single ordinal variable.

To minimize potential bias arising from undiagnosed cancer that might have influenced the activity level of alumni in 1977, we next conducted additional analyses that excluded the first 3 years, arbitrarily chosen, of follow-up. We also examined, separately, men aged ⩽55 and >55 years in 1977.

We then examined two groups of alumni separately: non-smokers or former smokers and heavy smokers who smoked >20 cigarettes daily. In the former group, we adjusted for age and body mass index; in the latter, we additionally adjusted for the number of cigarettes smoked daily.

Finally, we examined the associations of each of the different components of physical activity with lung cancer risk. In these analyses, we simultaneously included indicator terms for categories of walking, stair climbing, light (<4.5 MET) energy expenditure and energy expenditure from activities of at least moderate intensity (⩾4.5 MET), all classified as described above, in a single model.

Results

Table 1 describes the characteristics of alumni, according to their physical activity at baseline in 1977. The mean age of men at study entry was 58.3 years. Those more active were younger, were less likely to smoke cigarettes at baseline and had a lower body mass index.

Table 2 Incidence rates and relative risks of lung cancer among Harvard alumni, 1977–1993, according to physical activity in 1977

Physical activity[a] (kJ/week)	No. of events	Incidence rate[b] (per 10 000)	Relative risk[c] (95% CI)
<4200	102	15.9	1.00 (referent)
4200–8399	70	12.5	0.87 (0.64–1.18)
8400–12 599	38	11.0	0.76 (0.52–1.11)
⩾12 600	35	8.3	0.61 (0.41–0.89)
			P trend = 0.008

[a] Estimated from walking, climbing stairs and participating in sports or recreational activities.

[b] Age-adjusted.

[c] Adjusted for age (single years), cigarette smoking (non-smoker, smoker of ⩽20 cigarettes/day, smoker of >20 cigarettes/day, or smoker of unknown amount, assessed in 1977), and body mass index (<22.5, 22.5–<23.5, 23.5–<24.5, 24.5–<26.0, or ⩽26.0 kg/m^2).

During follow-up from 1977 through 1993, 245 men developed lung cancer in 196 798 person-years. The lung cancer incidence rate among alumni was much lower than among the general US population,[16] which was expected, since the prevalence of smoking among alumni (17.4%) was much lower than in the general population of that era (36.5% among US white men, 1979).[17]

Table 2 shows that higher levels of total energy expenditure were associated with lower lung cancer incidence rates. Men who expended ⩾12 600 kJ/week had a significantly lower risk of developing lung cancer, compared with those expending only <4200 kJ/week (RR = 0.61, 95% CI : 0.41–0.89). When we adjusted more finely for cigarette smoking in 1977 (smoking habit [never, past or current smoker], daily number of cigarettes smoked and duration of smoking), findings were similar, with corresponding RR of 1.00 (referent), 0.86, 0.76 and 0.60, respectively. Controlling for these smoking variables in 1977

Table 3 Incidence rates and relative risks of lung cancer among Harvard alumni, 1977–1993, according to different physical activity components in 1977

Physical activity component	No. of events	Incidence rate[a] (per 10 000)	Relative risk[b] (95% CI)
Distance walked (km/week)			
<5	101	16.5	1.00 (referent)
5 to <10	49	12.0	0.76 (0.54–1.07)
10 to <20	55	10.7	0.71 (0.51–0.99)
⩾20	40	9.2	0.65 (0.45–0.94)
			P trend = 0.01
Stairs climbed (storeys/week)			
<10	86	17.4	1.00 (referent)
10 to <20	43	10.7	0.63 (0.44–0.92)
20 to <35	43	10.6	0.64 (0.44–0.93)
⩾35	73	11.0	0.74 (0.54–1.02)
			P trend = 0.08
Activities at <4.5 MET[c] (kJ/week)			
None	152	12.5	1.00 (referent)
1 to <1050	26	13.8	1.20 (0.79–1.83)
1050 to <2520	19	11.6	0.92 (0.57–1.48)
2520 to <5880	19	10.3	0.81 (0.50–1.32)
⩾5880	29	13.3	0.99 (0.66–1.48)
			P trend = 0.62
Activities at ⩾4.5 MET[c] (kJ/week)			
None	133	16.0	1.00 (referent)
1 to <1050	38	12.2	0.84 (0.58–1.22)
1050 to <2520	19	8.3	0.64 (0.39–1.04)
2520 to <5880	33	11.4	0.93 (0.62–1.39)
⩾5880	22	7.2	0.60 (0.38–0.96)
			P trend = 0.046

[a] Age-adjusted.

[b] Adjusted for age (single years), cigarette smoking (non-smoker, smoker of ⩽20 cigarettes/day, smoker of >20 cigarettes/day, or smoker of unknown amount, assessed in 1977), body mass index (<22.5, 22.5–<23.5, 23.5–<24.5, 24.5–<26.0, or ⩽26.0 kg/m^2), and the other three components of physical activity (categorized as in the Table).

[c] Multiples of resting metabolic rate.

and updating them in 1988 yielded almost identical results, with corresponding RR of 1.00 (referent), 0.86, 0.77 and 0.60, respectively.

We then excluded the first 3 years of follow-up to minimize potential bias from alumni who may have changed their activity level because of undiagnosed cancer. Findings were similar; the corresponding RR were 1.00 (referent), 0.95, 0.76 and 0.62, respectively; *P* trend = 0.01.

Among men aged ⩽55 years at study entry (n = 6150), 50 lung cancers developed during follow-up. The RR of lung cancer associated with the four categories of total energy expenditure, adjusted for the same variables in Table 2, were 1.00 (referent), 1.19, 1.13 and 0.69, respectively; *P* trend = 0.48. Among those aged ⩾55 years at baseline (n = 7755), 195 lung cancers occurred. Corresponding RR were 1.00 (referent), 0.81, 0.67 and 0.59, respectively; *P* trend = 0.007.

Next, we examined the association of total energy expenditure with lung cancer risk among non-smokers or former smokers (n = 11 492) and heavy smokers (>20 cigarettes/day; n = 1110), separately. A total of 128 and 79 lung cancers developed in the two groups, respectively. We observed similar associations in the two groups, although findings in the latter were not significant, possibly due to lack of statistical power. Among non-smokers or former smokers, the RR of lung cancer associated with the four categories of total energy expenditure, adjusted for age and body mass index, were 1.00 (referent), 0.88, 0.83 and 0.54, respectively; *P* trend = 0.03. Among heavy smokers, after additionally adjusting for the number of cigarettes smoked daily in 1977, the corresponding RR were 1.00 (referent), 0.91, 0.92 and 0.61, respectively; *P* trend = 0.24.

Finally, we investigated the different components of physical activity contributing to total energy expenditure (Table 3). In these analyses, each component was adjusted for the other components of physical activity, in addition to age, smoking, and body mass index. There was a significant trend of declining lung cancer risk with greater distance walked (*P* = 0.01). Men walking at least 10 km/week were at significantly lower risk than those walking <5 km/week. Climbing stairs was also associated with a decreased risk, with significantly lower risk observed among men climbing 10 to <20 storeys/week but no further decrement among men climbing more stairs. With regard to physical activity intensity, sports and recreational

activities of at least moderate intensity, but not light intensity, were associated with lower lung cancer rates (P trend = 0.046 and 0.62, respectively). As before, finer control for cigarette smoking in 1977, as well as updating information on smoking in 1988, resulted in similar findings.

Discussion

These data indicate that physical activity appears to be inversely associated with lung cancer incidence rates among men. The inverse association was clear among men >55 years old; there were too few cases occurring in younger men for definitive conclusions. We observed similar associations among non-smokers or former smokers and among heavy smokers, although findings in heavy smokers were not statistically significant, possibly due to small numbers. When we examined the kinds of physical activity that were associated with lower lung cancer risk, we found walking, climbing stairs and participating in activities of at least moderate intensity (≥4.5 MET) contributed to the reduced risk, independent of the other activity components. However, light intensity activities (<4.5 MET) did not predict lower risk. These data extend our previous observations of an inverse association between total energy expenditure and lung cancer risk when following Harvard alumni during an earlier time period.[5]

There have been few previous studies investigating physical activity and lung cancer risk. In the Honolulu Heart Study, the most active one-third of men had a 30% lower risk of lung cancer compared with the least active one-third.[18] When physical activity at work and at home/recreation were examined separately, in both instances active men had somewhat lower risks than inactive men that did not achieve statistical significance. In another study of the US civilian population, men who reported being very active during their non-recreational time had half the lung cancer risk of those reporting that they were inactive.[19] However, no difference was noted between men who were very active or inactive during their recreation. A recent study of Norwegian men and women observed that physical activity was inversely related to lung cancer risk in men, but not women.[4] The RR of lung cancer among men walking, bicycling, or carrying out other recreational activities for ≥4 h a week, compared with those sedentary, was 0.75. A comparable finding was noted in the present study: Alumni who expended 8400–12 599 kJ/week also had a similar RR (0.76 compared with <4200 kJ/week); this level of energy expenditure can be achieved by ≥4 h of walking/jogging or bicycling.

In contrast, men and women in the Cancer Prevention Study II who reported heavy amounts of exercise at work or play had somewhat higher (though not significantly so) risks of lung cancer than those exercising in moderate amounts.[20] In another study of only occupational physical activity, investigators observed a significant trend of increasing lung cancer risk with increasing physical activity.[21] In this latter study, occupational physical activity may not have been a good proxy for total physical activity.

Are the findings from epidemiological studies that have observed physical activity to decrease lung cancer risk valid? The biggest concern is confounding by cigarette smoking, a strong predictor of lung cancer risk. In our main analyses, we adjusted for cigarette smoking status in 1977 in four categories only (non-smoker, current smoker of ≤20 cigarettes per day, >20 cigarettes per day, or unknown amount). However, in additional analyses where information was available for a subset of 11 849 men, we found similar results when adjusting for smoking in 1977 in more detail (smoking habit [never, past or current smoker], daily number of cigarettes smoked and duration of smoking). Updating these variables as of 1988 yielded similar findings as well. Therefore, it is unlikely that the results of the present study reflect confounding by cigarette smoking.

All other studies of physical activity and lung cancer risk, except for the Cancer Prevention Study II, did adjust for cigarette smoking to varying degrees. The possibility of residual confounding exists, although this is made less likely by two observations. First, in both non-smoking Harvard alumni as well as heavy smokers, active men had lower risks of lung cancer than those less active. While the finding was not significant among heavy smokers as a likely consequence of small numbers, in the Norwegian study where the prevalence of smoking was higher, investigators did observe a significant inverse association between physical activity and lung cancer risk among heavy smokers.[4] Second, if residual confounding accounted for the inverse association, we would expect a stronger inverse association with squamous cell carcinoma, the histological subtype most strongly related to cigarette smoking,[22] than with other histological subtypes. In the Norwegian study, inverse associations were noted for adenocarcinoma and small-cell carcinoma, but not squamous cell carcinoma.[4] Hence, residual confounding is less likely to explain the inverse association.

Another alternate explanation is confounding by diet. Individuals who are active are also more likely to consume a diet rich in fruits and vegetables. We did not have information on diet in 1977 and, thus, could not control for this. None of the other existing studies adjusted for diet as well, although one study did account for total energy and fat intake.[19] In the present study, we adjusted for body mass index since physically active individuals are leaner and leanness may be associated with increased lung cancer risk.[23] However, body mass index may not have reflected lean body mass accurately. A final concern is that undiagnosed lung cancer may cause individuals to become inactive, resulting in a spurious inverse association. However, we continued to observe the same findings when we attempted to minimize this bias by excluding the first three years of follow-up.

Biologically, it appears plausible for physical activity to decrease lung cancer rates. Physical activity has been shown to enhance immune function.[24,25] Additionally, as the Norwegian investigators proposed, the increased pulmonary function that occurs with higher levels of physical activity may result in decreased opportunity for interaction between inhaled carcinogens and the airways.[4]

In conclusion, the data from this study indicate that physical activity is associated with lower risk of lung cancer among men. The data also suggest that an energy expenditure of 12 600 kJ/week, achievable by perhaps 6–8 h of at least moderate intensity physical activity, can significantly lower risk. Further studies in other populations are required to confirm these observations. However, cigarette smoking is a far stronger predictor of lung cancer development than physical inactivity. The difference in

lung cancer risk between alumni who were heavy smokers and non-smokers or former smokers was almost 10-fold, compared to less than a twofold difference between the least and most active alumni.

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