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PHYSICAL ACTIVITY AND LUNG CANCER RISK IN MALE SMOKERS

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We examined the association between physical activity and lung cancer in a prospective cohort of 27,087 male smokers, ages 50–69 years, enrolled in the Alpha-Tocopherol, Beta Carotene Cancer Prevention (ATBC) Study. After an average of 10 years of follow-up, 1,442 lung cancer cases were diagnosed. Cox proportional hazards models were used to estimate the relative risk (RR) and 95% confidence intervals (CI) of lung cancer associated with self-reported occupational and leisure-time activity, adjusted for age, supplement group, body mass index, cigarettes smoked daily, years of smoking, education, energy intake and vegetable intake. There were no associations between occupational, leisure-time or combined categories of physical activity with lung cancer risk; however, age appeared to modify the effect of leisure-time activity ($p = 0.02$). Within increasing quartiles of age, the RRs (CI) for men active in leisure time compared to sedentary men were 0.77 (0.54–1.09), 0.74 (0.57–0.95), 1.09 (0.89–1.33) and 1.03 (0.88–1.21). These data suggest that among smokers, neither occupational nor leisure-time activity is associated with lung cancer risk. There may, however, be some modest risk reduction associated with leisure activity among younger smokers.
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To date, few studies have examined the relationship between physical activity and lung cancer. Of those studies, the majority reported that increased physical activity was associated with lower risk,[1–5] with some exceptions.[6,7] These investigations have varied in study design, population characteristics and types of activity and methods used to assess them. Although it is not clear how physical activity may lower lung cancer risk, potential mechanisms include increased functioning of the pulmonary or immune systems resulting from regular physical activity.[3,4]

Given that the magnitude of the effect of cigarette smoking on lung cancer far outweighs that of other risk factors,[8] smoking behavior must be appropriately considered in etiologic studies of lung cancer. Previous studies of physical activity have included current, former and nonsmokers, with the proportion of current smokers ranging from approximately 17%[4] to approximately 49%.[3] Despite adjustment for smoking in these studies, there exists the possibility of residual confounding, as smoking and exercise behaviors have been shown to be inversely related, albeit modestly.[9,10] Previous studies have not had adequate numbers of smokers and nonsmokers to examine interactions of smoking status and physical activity behaviors. For these reasons, the activity-lung cancer association may be more clearly addressed in a group that is homogenous with regard to smoking habits.

The purpose of our study was to examine the relationship between physical activity and lung cancer risk in a cohort of smokers. In this large, prospective study of middle-aged Finnish male smokers, we examined the associations for both occupational and leisure-time physical activities. We also looked at age and smoking characteristics as potential modifiers of this association.

MATERIAL AND METHODS

Study population

The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study was a randomized placebo-controlled trial that evaluated the effect of supplementation with α-tocopherol, β-carotene or both on the incidence and mortality related to lung and other cancers. The cohort consisted of 29,133 white males, aged 50–69 years, who smoked 5 or more cigarettes per day and lived in southwestern Finland. Subjects were recruited from 1985–1988 and randomized to 1 of 4 intervention groups: 50 mg/day α-tocopherol, 20 mg/day β-carotene, both α-tocopherol and β-carotene or placebo. At the start of the trial and at follow-up visits, study nurses informed the subjects of the dangers of smoking and asked them to make efforts to stop (19% quit for at least 8 months). The intervention ended on 30 April 1993, with postintervention cancer surveillance of the cohort continuing. Men who had been previously diagnosed with cancer, were alcoholics, had cirrhosis of the liver, severe angina with exertion, chronic renal insufficiency or were receiving anticoagulant therapy were excluded prior to randomization. Those taking supplements of vitamins E or A or β-carotene in excess of defined amounts also were not eligible to participate. The ATBC Study was approved by the institutional review boards of the National Cancer Institute (US) and the National Public Health Institute of Finland. Further details of the study have been described.[11] The number of men eligible for the current analysis was reduced by the availability of information on diet ($n = 27{,}111$; 93%) and other cofactors, resulting in 27,087 available in the occupational activity analysis and 27,082 in the leisure-time analysis.

Case identification

Incident cases of lung cancer (ICD9 code 162) diagnosed between randomization and 30 April 1997 were identified through the Finnish Cancer Registry. Medical records were centrally reviewed by study clinicians for all cases. Histologic or cytologic classification, using ICD0 classification, was available for cases diagnosed during the intervention period (94% of all cases). Of those classified, 50% were of squamous cell type, 27% were of small cell type, 19% were adenocarcinomas and 4% were of other cell types. Within our study population of men with complete covariate information, there were 1,442 cases for the occupational activity analysis and 1,441 for the leisure activity analysis.

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Data collection

At baseline, subjects completed a general medical history questionnaire and provided a blood sample. Usual occupational and leisure-time physical activity was assessed based on 2 questions. The first question asked the respondent to describe his activity during his work in the past year as: *(i)* not working; *(ii)* mainly sitting (*e.g.,* office worker, watchmaker); *(iii)* walking quite a lot but not lifting or carrying (*e.g.,* foreman, shop assistant); *(iv)* walking and lifting (*e.g.,* carpenter, cattle tender); or *(v)* heavy physical work (*e.g.,* forestry work, heavy farmwork). The second question asked the respondent to describe his usual leisure-time activity in the past year as: *(i)* sedentary (*e.g.,* reading, watching television); *(ii)* moderate (*e.g.,* walking, hunting, gardening) fairly regularly; or *(iii)* heavy (*e.g.,* running, skiing, swimming) fairly regularly**.** A specific list of occupations in which lung cancer risk factor exposures may be higher was included on the questionnaire, and participants were asked to indicate if they had worked in any of those occupations. Participants were then crudely classified as occupationally exposed to asbestos or not and as exposed to other lung cancer risk exposures such as mining or quarrying. Participants also completed a self-administered food-use questionnaire in which subjects reported usual frequency of consumption and portion size of more than 276 food items, mixed dishes and beverages during the previous 12 months.

Statistical analysis

In all analyses, sedentary men were used as the reference group, and the nonworkers were kept as a separate occupational activity category because "nonworking" is not a well-defined physical activity category, and in the case of our study, included retirees. Due to the small number of subjects reporting regular, heavy leisure-time physical activity (approx. 6%), and the similarity in risk estimates for the heavy and moderate categories, they were combined to create an "active" leisure group. Cox proportional hazards models were used to estimate the relative risk (RR) and 95% confidence intervals (CI) of lung cancer associated with level of physical activity with follow-up time as the underlying time metric. All models were adjusted for intervention group (alpha-tocopherol, yes/no; beta-carotene, yes/no) given that the main results of the trial showed slightly higher lung cancer incidence among the men given beta-carotene supplementation.[12] Models were also adjusted for those variables producing a ≥10% change in the beta coefficients of the physical activity variables, including age, body mass index (BMI, kg/m^2), cigarettes smoked/day and years of smoking (all continuous), education (≤elementary, junior high, ≥senior high), daily energy intake (kcal; quartile) and energy-adjusted vegetable intake (g; quartile) using the residual method of Willett and Stampfer.[13] Age and level of smoking were assessed as effect modifiers of the association between lung cancer and activity by including their cofactor-activity cross-product terms in separate models and also through stratified analyses. All models were also run excluding the first 2 years of follow-up, with no significant changes in any of the estimates. The validity of the proportional hazards assumption was checked by examining the cross-product terms of follow-up time and the covariates of interest, and there were no departures from this assumption for any covariate in the final models.

RESULTS

Selected participant characteristics are depicted in Table I according to level of occupational and leisure-time physical activity. Nonworkers constituted 42% of the cohort and were older than working men. Compared to the sedentary workers, the nonworkers were older, had smoked longer, were less educated, tended to eat fewer vegetables and more of them had been exposed to asbestos and other high lung cancer risk exposures (mining, quarrying, etc.) when they were working. Men in the moderate and heavy occupational activity categories were similar to nonworking men with regard to having had less education and greater asbestos and other occupational exposures. Although daily energy intake increased with level of occupational physical activity, daily vegetable intake, unadjusted for calories, actually decreased. Fifty-eight percent of the cohort reported participating in physical activity during their leisure time. These active men tended to smoke fewer cigarettes/day, inhale smoke less often and had greater dietary energy and vegetable intakes.

We observed no inverse association between occupational physical activity and risk of lung cancer in this cohort (Table II). There was, however, a modest increase in lung cancer risk suggested among the men in the heavy occupational activity category (not statistically significant). In addition, nonworkers appeared to be at increased risk, a finding that remained unchanged when the first 2 years of follow-up were excluded from analysis (RR = 1.27; CI = 1.02–1.57). When analyzed by histologic subtype, the associations did not change appreciably (data not shown). There was no association between leisure-time physical activity and lung cancer risk in these smokers, nor were there any associations for the combined categories of occupational and leisure-time activity (Table II). Leisure-time activity was further examined in relation to the spe-

TABLE I – SELECTED BASELINE CHARACTERISTICS BY LEVEL OF LEISURE-TIME AND OCCUPATIONAL PHYSICAL ACTIVITY[1]

Characteristic[2]	Occupational activity					Leisure-time activity	
	Nonworker (n = 11,327)	Sedentary (n = 3,803)	Light (n = 5,020)	Moderate (n = 4,498)	Heavy (n = 2,439)	Sedentary (n = 11,244)	Active (n = 15,838)
Age (years)	60.3 ± 4.8	54.9 ± 3.9	54.9 ± 3.9	54.7 ± 3.8	55.6 ± 4.4	57.1 ± 5.1	57.2 ± 5.1
Cigarettes/day	19.0 ± 8.3	22.2 ± 9.8	21.2 ± 9.1	21.5 ± 8.4	20.7 ± 8.6	21.7 ± 9.2	19.6 ± 8.4
Years smoked	39.4 ± 8.1	33.4 ± 7.8	33.0 ± 7.9	33.7 ± 7.4	34.0 ± 7.9	36.4 ± 8.2	35.6 ± 8.5
Age started smoking (years)	19.2 ± 4.6	19.8 ± 4.6	19.8 ± 4.7	19.4 ± 4.6	19.8 ± 5.1	19.2 ± 4.6	19.7 ± 4.7
Always inhale when smoking (%)	54	54	51	52	52	58	49
Asbestos exposure (%)	2.4	0.8	1.5	3.2	2.1	2.0	2.1
Occupational exposure (%)	20.0	10.7	15.4	20.1	20.3	17.4	18.2
Education (% > elementary)	16.0	47.5	32.1	11.1	5.9	22.1	21.5
Active in leisure (%)	60.5	54.7	61.9	57.7	49.9	—	—
Not working (%)	—	—	—	—	—	39.9	43.2
BMI (kg/m^2)	26.2 ± 3.9	26.7 ± 3.9	26.3 ± 3.6	26.1 ± 3.6	26.1 ± 3.5	26.5 ± 4.1	26.1 ± 3.5
Energy (kcal/d)	2,703 ± 770	2,705 ± 728	2,792 ± 741	3,014 ± 812	3,189 ± 813	2,785 ± 807	2,836 ± 772
Vegetable (g/d)	135 ± 101	192 ± 128	182 ± 118	151 ± 109	123 ± 88	139 ± 108	163 ± 112
Alcohol[3] (g/d)	9 (0–56)	14 (0–63)	13 (0–58)	13 (0–62)	9 (0–56)	12 (0–67)	10 (0–53)

[1]Mean ± standard deviation or percent of group.–[2]Definitions: BMI, body mass index; asbestos exposure, occupational exposure to asbestos; occupational exposure, worked in an occupation with other high-risk exposures such as mining or lead refining.–[3]Median (95% CI).

TABLE II – RELATIVE RISK (95% CI) OF LUNG CANCER BY OCCUPATIONAL AND LEISURE-TIME PHYSICAL ACTIVITY CATEGORIES[1]

Variable	No. of cases	Person years[2]	RR (95% CI)	*p* for trend[3]
Occupational activity				
Nonworker	826	96,641	1.27 (1.04–1.56)	—
Sedentary	133	36,197	1.0	Reference
Light	181	48,010	1.01 (0.81–1.27)	
Moderate	184	42,614	1.09 (0.86–1.37)	
Heavy	118	22,546	1.23 (0.95–1.59)	0.12
Leisure-time activity				
Sedentary	630	100,306	1.0	Reference
Active	811	145,659	0.97 (0.87–1.07)	—
Combined activity (O/L)				
Sedentary/sedentary	69	16,246	1.0	Reference
Sedentary/active	64	19,940	0.86 (0.61–1.21)	—
Light/sedentary	83	18,192	1.04 (0.75–1.43)	
Light/active	98	29,809	0.87 (0.64–1.19)	0.39
Moderate/sedentary	86	17,775	1.05 (0.76–1.45)	
Moderate/active	97	24,834	0.97 (0.70–1.32)	0.74
Heavy/sedentary	62	11,212	1.12 (0.78–1.59)	
Heavy/active	56	11,317	1.17 (0.82–1.68)	0.48
Nonworker/sedentary	329	36,859	1.18 (0.90–1.55)	
Nonworker/active	496	59,738	1.18 (0.91–1.54)	0.38

[1]Models are adjusted for age, supplement group, body mass index, cigarettes smoked/day, years of smoking, education, energy intake and vegetable intake.–[2]Total person years for cases and noncases in category of activity.–[3]The tests for trend use the sedentary group as the reference category. Nonworkers are not included in the trend test in the occupational activity analysis. In the combined analysis, tests for trend are performed within occupational activity group across increasing leisure activity, with sedentary at both occupation and leisure as the referent group.

TABLE III – RELATIVE RISK (RR) AND 95% CONFIDENCE INTERVAL (95% CI) OF LUNG CANCER FOR PERSONS ACTIVE IN THEIR LEISURE *VS.* THOSE SEDENTARY IN LEISURE-TIME, BY QUARTILE OF AGE, QUARTILE OF SMOKING (YEARS) AND BY CATEGORY OF CIGARETTES/DAY OF SMOKING[1]

Variable	No. of cases	Person years	RR (95% CI)	p_{int}[2]
Age (years)				
50–52	134	57,764	0.77 (0.54–1.09)	0.02
53–56	244	69,371	0.74 (0.57–0.95)	
57–60	403	57,737	1.09 (0.89–1.33)	
61–69	660	61,092	1.03 (0.88–1.21)	
Cigarettes/day				
≤19	397	89,301	1.06 (0.86–1.31)	0.25
20	457	75,499	0.99 (0.82–1.19)	
≥20	587	81,164	0.91 (0.77–1.07)	
Years of smoking				
1–30	116	62,283	0.83 (0.57–1.21)	0.26
31–36	223	66,525	0.79 (0.61–1.03)	
37–41	423	59,122	1.14 (0.94–1.39)	
42–61	679	58,035	0.95 (0.82–1.11)	

[1]Models are adjusted for age, supplement group, body mass index, cigarettes smoked/day, years of smoking, education, energy intake and vegetable intake.–[2]*p*-value for interaction.

cific histologic subtypes of lung cancer. The RRs and 95% CI for squamous cell carcinoma, small cell carcinoma and adenocarcinoma were 0.93 (0.79–1.10), 1.05 (0.84–1.31) and 0.96 (0.73–1.25), respectively, for active compared to sedentary men.

The occupational and leisure-time associations were further examined by level of age, years of smoking and the number of cigarettes smoked daily. The risk estimates for the occupational categories were not appreciably different across categories of these factors (data not shown). Age, however, appeared to modify the relationship between leisure-time activity and lung cancer (Table III). Among the younger men in the cohort, there was an approx. 20–25% lower risk for active compared to sedentary men, whereas no risk reduction was evident among older men. Further adjustment for occupational activity did not change the risk estimates. To determine if younger "active" men participated in more heavy exercise than the older "active" men, level of leisure-time activity was examined within the quartiles of age. The percentage of men participating in regular heavy exercise was 6.9, 5.7, 5.3 and 6.1% for increasing age quartiles. The percentage of men who quit smoking (at least 8 months) also did not vary substantially by age quartile among the active men and was actually highest in the older men (18, 19, 20 and 22% for increasing quartiles). Neither the number of cigarettes smoked nor years of smoking modified the leisure-time/physical activity association.

DISCUSSION

The results of our study suggest that neither occupational nor leisure-time physical activity is associated with the risk of lung cancer in long-term cigarette smokers. Neither age nor amount of smoking modified the occupational physical activity association. For leisure-time physical activity, there appeared to be a modest inverse association associated with higher activity levels among the younger men that was not apparent in the older men.

The lack of an inverse association for occupational activity is consistent with most[2,3,6,7] but not all[1] studies that have examined this activity class specifically. In particular, Thune and Lund, who used a similar activity classification, also observed no association with occupational activity.[3] Our occupational activity categories were associated with education level and vegetable intake, as well as asbestos and other high lung cancer risk occupational exposures (see Table I). Whereas we controlled for education and vegetable intake in our models, further adjustment for asbestos and the other high-risk exposures did not appear to change our risk estimates. Despite our attempts to control for their influence, there may still be residual confounding from these and/or other factors in our risk estimates. Any beneficial effect of occupational activity may be outweighed by the related increase in risk due to these other factors, and indeed, we saw a nonsignificant 23% increase in risk in the men in the heaviest occupational activity category. This is consistent with a previous case-control study of occupational activity and lung cancer risk by Brownson *et al.,* which found a significant 20% lower risk for men in sedentary occupations compared to those engaged in high occupational activity.[7] Interestingly, we found that high occupational activity is associated with a decreased risk of colon cancer in this same cohort,[14] which is also similar to that seen in the colon cancer analysis by Brownson *et al.*[7] These results imply that occupational categorization of activity may be related to other lung cancer, but not colon cancer, risk factors. The relationship between this type of categorization and other potential cancer risk factors should be considered carefully when evaluating the occupational physical activity and lung cancer literature.

Our analysis revealed similar risk estimates for nonworkers and workers in jobs requiring moderate to heavy physical labor. We have previously seen similarities in risk estimates for these groups with respect to colorectal cancer.[14] Given that education and degree of asbestos and other occupational exposures are somewhat similar for the older nonworking men and the men in the moderate and heavy occupational activity categories, we hypothesize that the nonworking category may largely consist of men retired from occupations requiring moderate to heavy physical activity. Alternatively, the nonworkers may have been unemployed due to smoking-related illnesses; however, exclusion of the first 2 years of follow-up did not change the risk estimates, arguing against this explanation.

In contrast to our study, others have found beneficial associations between lung cancer and either leisure-time or indices of total physical activity.[2–4] Given the nature of our cohort, comparisons may best be made to those studies that have looked at the association in smokers in particular. Thune and Lund[3] found a stronger inverse association for leisure activity among men who smoked $\geq$15 cigarettes/day than for men who smoked $<$15 cigarettes/day. There were similar risk reductions associated with increased activity for nonsmokers/former smokers combined, as there were for heavy smokers ($>$20 cigarettes/day) in the study by Lee *et al.*,[4] although the findings in the heavy smokers were not statistically significant. The reductions in risk associated with higher activity among heavier smokers in these studies are not consistent with our results.

Our analysis suggested that younger smokers who are active might have a lower risk of lung cancer compared to their sedentary peers but that this same lower risk is not seen in older smokers. The only study to date that has looked at the association by age found inverse associations for both groups of men ($<$55 and $\geq$55 years of age), with the lowest risks associated with physical activity among the older men; however, that cohort consisted mostly of nonsmokers.[4] It may be that among older smokers, who have presumably accumulated more carcinogenic insults, any small influence of increased physical activity cannot be seen. Alternatively, within the category of "active," the older men in our analysis could have been less vigorously active—or engaged in somewhat different activities—compared to the "active" younger men. When we looked at the percentage of each age quartile that reported being vigorously active, however, there was no clear difference by age, suggesting there was little age-related variation or that our simple activity question may not have accurately discriminated among levels or types of leisure-time activity.

There are several possible explanations for the difference between our study and some of the prior cohort studies. Our present investigation was large, including 27,000 male smokers, and has substantial power based on more than 1,400 incident lung cancers, more than any other study to date. On the other hand, our findings may not be generalizable, given that these men were long-term smokers who had volunteered for a clinical trial. The men in our study appear to have smoked more years and more cigarettes/day than did smokers in the previous studies. More studies are needed that examine the physical activity and lung cancer association in different populations, particularly nonsmokers. Our cohort also presumably had very different occupational exposures compared to the Harvard University alumni in the study of Lee *et al.*,[4] a likelihood made more relevant given the relationship between activity and other important lung cancer risk factors. Finally, our measures of physical activity were limited to 1 question each for occupational and leisure-time activity at 1 point in time, since this was not a primary purpose of the ATBC trial. This limited physical activity assessment may explain the null results shown here. Thune *et al.*,[3] using a similar questionnaire, showed a significant 61% lower risk for men who reported regular leisure-time exercise in their study at both baseline and 3–5 years later, but only a nonsignificant 16% lower risk for men regularly exercising at baseline. Given the latency period for the development on lung cancer, etiologic studies must consider this issue when determining the appropriate age/time at which to assess activity. There is a clear need for more studies that are designed to evaluate physical activity at different ages and that use more thorough questions that allow for determinations of the types, durations, intensities and frequencies of exercise associated with lung cancer risk.

Strengths of our study include its prospective nature and the number of cases available for analysis. We also had dietary data, allowing us to control for confounding effects of energy and vegetable intakes in these analyses, which prior studies have not done. Since smoking is the strongest risk factor for lung cancer, and since approx. 87% of lung cancer deaths can be attributed to cigarette smoking,[8] the homogeneity of tobacco exposure in our cohort would appear to be an advantage over previous studies, where residual confounding despite control for more varying tobacco exposure remains a possibility.

In summary, our results suggest that there is no association of either occupational or leisure-time activity with lung cancer risk in this group of smokers as a whole. There may, however, be a protective relationship for leisure physical activity among younger smokers. Further investigation of the association in diverse populations, with careful consideration of smoking status, is needed.

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