Physical Activity, White Blood Cell Count, and Lung Cancer Risk in a Prospective Cohort Study

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Abstract

Previous studies have suggested that physical activity may lower lung cancer risk. The association of physical activity with reduced chronic inflammation provides a potential mechanism, yet few studies have directly related inflammatory markers to cancer incidence. The relation among physical activity, inflammation, and lung cancer risk was evaluated in a prospective cohort of 4,831 subjects, 43 to 86 years of age, in Beaver Dam, Wisconsin. A total physical activity index was created by summing up kilocalories per week from sweat-inducing physical activities, city blocks walked, and flights of stairs climbed. Two inflammatory markers, WBC count and serum albumin, were measured at the baseline examination. During an average of 12.8 years of follow-up, 134 incident cases of lung cancer were diagnosed. After multivariable adjustment, participants in the highest tertile of total physical activity index had a 45% reduction in lung cancer risk compared with those in the lowest tertile (hazard ratio, 0.55; 95% confidence interval, 0.35-0.86). Participants with WBC counts in the upper tertile ($\geq 8 \times 10^3/\mu L$) were 2.81 (95% confidence interval, 1.58-5.01) times as likely to develop lung cancer as those with counts in the lowest tertile ($<6.4 \times 10^3/\mu L$). Serum albumin was not related to lung cancer risk. There was no evidence that inflammation mediated the association between physical activity and lung cancer risk, as the physical activity risk estimates were essentially unchanged after adjustment for WBC count. Although the potential for residual confounding by smoking could not be eliminated, these data suggest that physical activity and WBC count are independent risk factors for lung cancer. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2714–22)

Introduction

Lung cancer is the leading cause of cancer death among men and women in the United States (1). Strategies to reduce lung cancer risk besides smoking prevention and cessation are poorly understood. A number of epidemiologic studies have suggested that physical activity may reduce the risk of lung cancer (2-13), with a recent meta-analysis concluding that higher levels of leisure-time physical activity protect against lung cancer (14). In 2002, however, the IARC concluded that the evidence for an association between physical activity and lung cancer remained inconclusive, and two large studies recently found no consistent association between physical activity and lung cancer risk (15, 16).

The value of molecular biomarkers in discerning the relation between physical activity and cancer has recently been recognized (17, 18). The incorporation of biomarkers can be particularly helpful in clarifying inconclusive epidemiologic evidence and investigating potential mechanisms by which physical activity exerts its effects (17). A number of potential mechanisms through which physical activity may offer protection from lung cancer have been proposed. Physical activity and physical fitness are consistently observed to be associated with reduced chronic inflammation, reflected in lower levels of the inflammatory markers serum C-reactive protein, fibrinogen and WBC count, and increased levels of serum albumin (a negative acute-phase protein; refs. 19-23). Chronic inflammation has been hypothesized to be a risk factor for a wide range of cancers (24-26). Thus, physical activity could reduce lung cancer risk by reducing chronic inflammation. Yet few studies have directly evaluated markers of inflammation in relation to lung cancer incidence (27-30).

We investigated the relation between self-reported physical activity and lung cancer in an established cohort of older adults. Additionally, we measured two inflammatory markers, WBC count and serum albumin, in baseline blood samples to evaluate whether inflammation mediates the relation between physical activity and lung cancer.

Materials and Methods

Study Population. Descriptions of the population and the methods used to identify the population have been previously published (31-33). Briefly, a private census of the population living in Beaver Dam, Wisconsin, was done by the University of Wisconsin Extension-Survey Research Laboratory between September 15, 1987, and May 4, 1988. Eligibility requirements for entry into the study included living in the city or township of Beaver

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Dam and being 43 to 84 y of age at the time of the census. A total of 5,925 eligible individuals were identified who met the criteria.

Of the 5,925 eligible individuals, 4,926 (83.1%) participated in the study examination, including 2,166 men and 2,760 women. The reasons for nonparticipation included 225 deaths (3.8%) before the examination, moving out of the area by 91 people (1.5%), failure to locate 23 people (0.4%), and refusal to participate by 391 (6.6%). Eligible participants who completed telephone interviews but were not examined (n = 269; 4.5%) were not included in this analysis, so that data were available for 4,926 participants who consented to examinations.

Case Identification. Incident cases of lung cancer (International Classification of Diseases for Oncology codes C34.0-34.9; ref. 34) diagnosed in study participants through July 2004 were identified through linkages with the Wisconsin Cancer Reporting System (the statewide mandatory tumor registry), Wisconsin death certificates, and the National Death Index. Deaths due to lung cancer identified through death records that were not also identified by the tumor registry (n = 7) were assigned a date of diagnosis equal to the average length of time from diagnosis to death for lung cancer cases in the Wisconsin tumor registry subtracted from their date of death (13 mo).

Data Collection. All participants provided signed informed consent at the time of the examination. Study questionnaires elicited information on comorbidities, reproductive and menstrual histories (for females), lifestyle factors, health history, medication histories, and demographics. Lifestyle factors on the questionnaires included physical activity, alcohol and caffeinated beverage consumption, smoking history, vitamin and mineral supplement use, and occupational history. Participants reported histories of diagnosis with major chronic medical conditions and surgical history. Collected demographic information included race/ethnicity and education, and participants were asked to report their marital status and income category.

To assess smoking history, subjects were asked if they had smoked more than 100 cigarettes in their lifetime, how many years they have smoked cigarettes, whether they smoke now, how long ago they stopped, and how many cigarettes they smoked per day (currently, or ''usually'' during smoking history for former smokers).

To assess physical activity, subjects were asked to report the number of city blocks walked per day (12 blocks = 1 mile), flights of stairs climbed per day, and the number of episodes of ''regular activity long enough to work up a sweat'' each week (35). A summary measure of total physical activity was created by summing the kilocalories (kcal) per week from blocks walked, flights of stairs climbed, and episodes of sweat-inducing activities. For 1 block walked per day and 1 flight of stairs climbed per day, we assigned 56 kcal/wk and 28 kcal/wk, respectively, as previously

Table 1. Selected participant characteristics at baseline according to physical activity levels

Characteristics at baseline	Episodes of sweat-inducing activities/wk (%)*		City blocks walked/d (%)*		Flights of stairs climbed/d (%)*	
	None (n = 3,215)	1 or more (n = 1,614)	None (n = 2,204)	1 or more (n = 2,610)	0-2 (n = 2,187)	3 or more (n = 2,639)
Age, y						
43-49	16	20	16	18	12	22
50-59	26	30	25	29	24	30
60-69	27	30	28	28	28	28
70-79	23	17	22	20	27	16
80-86	9	3	9	5	10	4
Sex						
Male	43	45	37	49	39	47
Female	57	55	63	51	61	53
Smoking status						
Never	45	45	47	43	46	44
Former	32	41	33	38	36	35
Current	23	14	21	19	18	21
Body mass index tertile (kg/m^2)						
1 (<26.2)	32	36	32	34	31	35
2 (26.2-30.3)	33	36	31	36	32	35
3 (>30.3)	35	29	36	30	36	30
Alcohol drinks/wk						
None	53	45	56	46	56	46
<5	20	28	20	25	21	24
≥5	26	27	24	29	23	29
Education, y						
<12	34	19	33	25	36	23
12	44	43	44	43	42	45
>12	22	38	23	32	22	32
Mean (SD) heart rate †	38.6 (5.9)	37.5 (5.8)	38.5 (6.0)	38.0 (5.8)	38.5 (6.0)	38.0 (5.8)
Mean (SD) WBC count (×10^3/μL)	7.5 (2.2)	7.1 (1.9)	7.5 (2.2)	7.3 (2.1)	7.6 (2.3)	7.2 (2.0)
Mean (SD) albumin (g/dL)	4.6 (0.4)	4.7 (0.3)	4.6 (0.4)	4.7 (0.4)	4.6 (0.4)	4.7 (0.4)

*Information regarding episodes of activity was missing for 2 participants, blocks walked was missing for 17 participants, and stairs climbed was missing for 5 participants.
†Thirty-second heart rate.

Table 2. HR and 95% CI of lung cancer according to physical activity levels and inflammatory markers

	No. cases	Person-years*	HR (95% CI) †	P_{trend} †	HR (95% CI) ‡	P_{trend} ‡
Episodes of sweat-inducing activities/wk						
0	105	36,753	1		1	
1-3	10	10,862	0.44 (0.23-0.85)		0.45 (0.23-0.87)	
≥4	19	9,611	0.75 (0.45-1.24)	0.08	0.76 (0.46-1.26)	0.09
City blocks walked/d						
0	73	25,117	1		1	
1-11	44	19,633	0.93 (0.63-1.37)		0.92 (0.62-1.35)	
≥12	17	12,292	0.53 (0.31-0.90)	0.03	0.52 (0.30-0.89)	0.02
Flights of stairs climbed/d						
0-1	44	17,715	1		1	
2-5	60	20,224	1.53 (1.02-2.29)		1.53 (1.02-2.29)	
>5	30	19,254	0.84 (0.52-1.36)	0.58	0.86 (0.53-1.40)	0.67
Total physical activity index (kcal/wk)§						
0-174	65	18,531	1		1	
175-874	38	19,120	0.72 (0.47-1.09)		0.72 (0.48-1.09)	
≥875	31	19,358	0.55 (0.35-0.86)	0.01	0.56 (0.35-0.87)	0.01
Heart rate (30 s)						
21-33	27	12,065	1		1	
34-42	70	33,925	0.93 (0.59-1.46)		0.95 (0.60-1.49)	
>42	37	11,235	1.30 (0.80-2.16)	0.27	1.25 (0.75-2.09)	0.35
WBC tertile ($\times 10^3/\mu L$)						
<6.4	16	19,605	1		—	
6.4-7.9	50	19,421	2.74 (1.53-4.90)		—	
≥8	68	18,019	2.81 (1.58-5.01)	0.001	—	
Albumin tertile (g/dL)						
<4.6	52	19,307	1		—	
4.6-4.8	51	20,321	1.02 (0.69-1.52)		—	
≥4.9	31	17,427	0.85 (0.54-1.34)	0.52	—	

*Total person-years for cases and noncases in category of activity.
†Models are adjusted for age, sex, pack-years of smoking, time since smoking cessation, body mass index, alcohol intake, and education.
‡Models are adjusted for all variables in †, plus WBC count.
§Kilocalories per week from city blocks walked, flights of stairs climbed, and sweat-inducing activities (see Materials and Methods).

used in the analyses of the Harvard Alumni Health Study (5, 6, 36). The duration and intensity of participation in sweat-inducing activities were not ascertained; a typical duration of 30 min at a multiple of resting metabolic rate of 7 was assumed (equivalent to jogging or tennis; ref. 37). Given a resting metabolic rate of 1 kcal/kg/h and the median subject weight of 76 kg, each sweat-inducing activity episode per week was assigned 266 kcal [= 7 × (1 kcal/kg/h) × (76 kg) × (0.5 h)].

Objective measures of comorbidity were collected in addition to self-reported chronic health conditions. Standardized procedures were used to measure height, weight, heart rate, vision, hearing, and blood pressure during the examination (31).

Laboratory Analysis. Casual venous blood specimens were obtained at the baseline examination for laboratory analysis. The collection, storage, and laboratory methods for the analysis of serum inflammatory markers have been previously described (38). Immediately after obtaining the baseline blood sample, WBC count was determined using the Coulter counter method, and serum albumin levels were determined by Technicon, Inc.

Statistical Analysis. Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence intervals (95% CI) of lung cancer associated with levels of physical activity and inflammatory markers. We tested proportionality assumptions and found no evidence of violation. Regression models were fitted according to the number of episodes of sweat-inducing activities, the number of blocks walked, the number of flights of stairs climbed, total physical activity index, heart rate, WBC count, and serum albumin level. With the exception of heart rate, the physical activity and inflammatory marker variables were categorized roughly by person-year tertiles, using round numbers as cutpoints. For sweat-inducing activities and city blocks walked per week, more than one third of person-years had zero activities. All models were adjusted for age (<50, 50-59, 60-69, 70-79, ≥80 y), sex, pack-years of smoking (none, tertiles), time since smoking cessation (never smoker, current smoker, quartiles), body mass index (kg/m^2, tertiles), alcohol intake (none, <5 drinks/wk, ≥5 drinks/wk), and education (<high school, high school degree, > high school). *P* values for trend were evaluated by including categorical variables in the models as continuous linear terms. Age and other covariates were assessed as effect modifiers of the association between physical activity and lung cancer by evaluating the change in the log-likelihood after including their cross-product terms in the regression models. In analyses stratified by smoking history, subjects were considered current smokers if they responded affirmatively to the questionnaire item ''Do you smoke now?'' and former smokers if they responded negatively but had smoked more than 100 cigarettes in their lifetime. Never and former smokers were combined in the stratified analysis because of insufficient numbers of each separately. Plots of cumulative lung cancer incidence according to the total physical activity index and WBC count were produced using the Kaplan-Meier method.

Least squared means and *P* values comparing WBC count and serum albumin according to tertiles of total physical activity index were calculated using multivariable ANOVA including covariates for smoking history. The mean levels of WBC count and serum albumin at baseline among participants who subsequently developed lung cancer were compared with levels corresponding to participants without lung cancer during the follow-up period using *t* tests. The values of albumin and WBC count were not transformed for the *t* tests because they were approximately normally distributed. *P* values using Wilcoxon nonparametric tests were essentially identical to those obtained using *t* tests, and are not shown.

Study participants reporting a personal history of lung cancer at the baseline examination ($n = 7$), or identified as a case of lung cancer within 12 mo of the baseline examination ($n = 6$), were excluded from the analysis. An additional 82 people who died within 12 mo of their baseline examination were also excluded from this analysis.

Results

During 62,062 person-years of follow-up (an average of 12.8 years per person), 134 cases of lung cancer were diagnosed among the 4,831 subjects without a personal history of lung cancer who survived at least 1 year after the baseline examination. Among cases, the mean time between baseline examination and diagnosis was 8.0 years (SD, 3.8; range, 1.2-16.3 years). According to

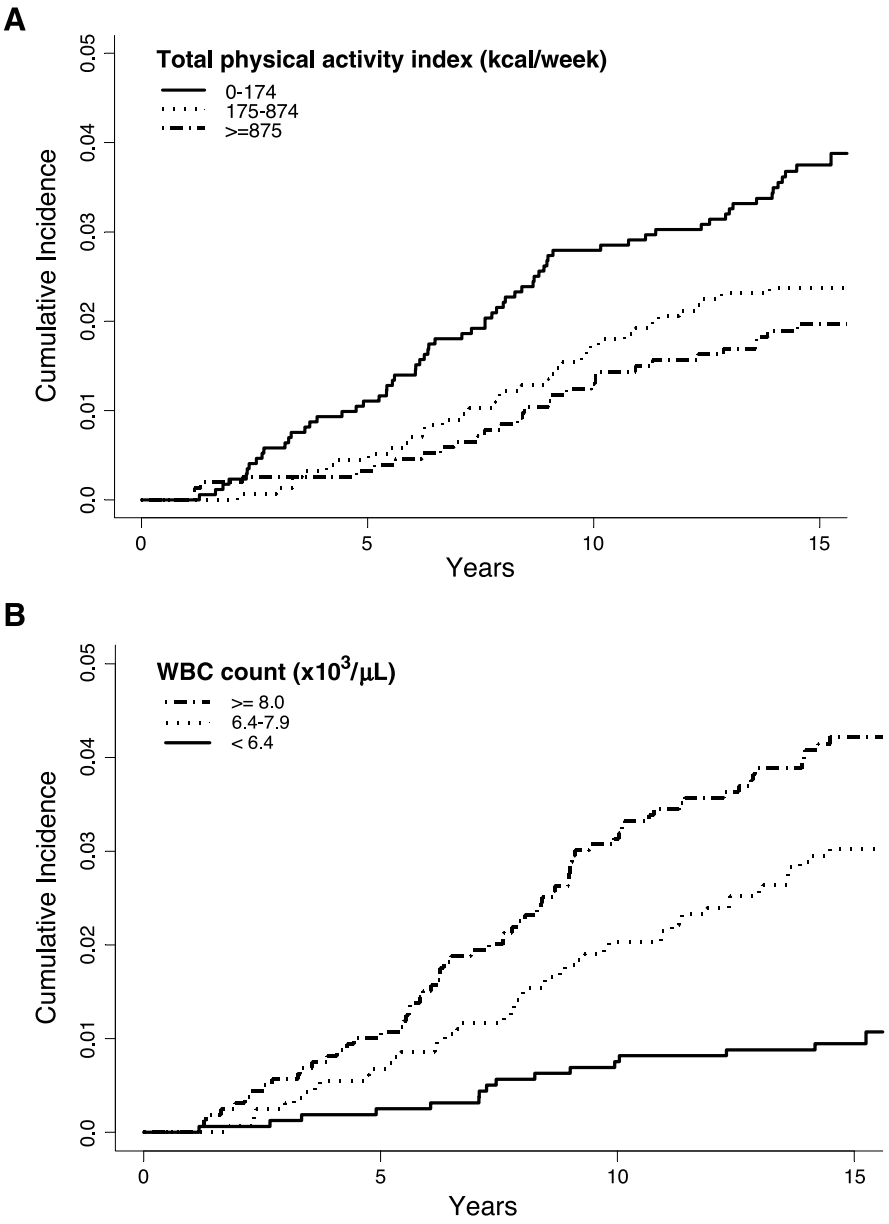

Figure 1. Lung cancer cumulative incidence according to total physical activity index (**A**) and WBC count (**B**). Note that lung cancer cases diagnosed within the first year following the baseline exam were excluded.

Table 3. HR and 95% CI of lung cancer according to physical activity by smoking status and gender

Total physical activity index (kcal/wk)*	No. cases	Person-years †	HR (95% CI) ‡	P_{trend} ‡
Current smokers				
0-174	36	4,052	1	
175-874	15	4,026	0.48 (0.26-0.91)	
≥875	12	3,107	0.49 (0.25-0.97)	0.02
Never/former smokers				
0-174	29	14,477	1	
175-874	23	15,081	0.97 (0.55-1.71)	
≥875	19	16,236	0.60 (0.33-1.11)	0.10
Females				
0-174	28	11,941	1	
175-874	17	10,737	1.02 (0.54-1.95)	
≥875	10	10,166	0.66 (0.30-1.44)	0.35
Males				
0-174	37	6,590	1	
175-874	21	8,383	0.56 (0.33-0.97)	
≥875	21	9,192	0.50 (0.29-0.87)	0.01

*Kilocalories per week from city blocks walked, flights of stairs climbed, and sweat-inducing activities (see Materials and Methods).
†Total person-years for cases and noncases in category of activity.
‡Models are adjusted for age, sex, pack-years of smoking, time since smoking cessation, body mass index, alcohol intake, and education.

tumor registry reports, 51% of the cases were non–small-cell type (23% adenocarcinoma, 14% squamous, 10% large cell, and 4% not otherwise specified), 12% were small-cell type, and 37% were unspecified-cell types. Of the cases, 23 (17%) were local, 27 (20%) were regional, 45 (34%) were distant, and 39 (29%) were unknown stage at diagnosis.

Physical activity variables are summarized according to other selected covariates in Table 1. In general, participants who were more active tended to be younger, have lower body mass, drink more alcohol, and report more years of education than less active participants. The distribution of participants according to smoking status within levels of physical activity depended upon the type of activity: current smokers were less likely to report vigorous activities that caused a sweat but more likely to climb stairs. Participants who were more active had lower heart rates and WBC counts than less active participants. After adjusting for smoking status, pack-years, and time since cessation, WBC counts declined in successive total physical activity index tertiles (7.6, 7.4, and 7.1 $\times 10^3/\mu L$, respectively; $P < 0.001$). No differences were observed in serum albumin according to physical activity levels.

Higher levels of physical activity at baseline were inversely associated with lung cancer incidence (Table 2; Fig. 1A). After multivariable adjustment for demographic and lifestyle factors (first column of HR), the risk of lung cancer was reduced by over 40% among participants reporting 12 or more city blocks walked per day (P_{trend} = 0.03) and those in the highest tertile of the total physical activity index (≥875 kcal/wk; P_{trend} = 0.01). There was a negative association between lung cancer risk and the weekly number of episodes of activity vigorous enough to cause a sweat, although a dose-response pattern was not observed (P_{trend} = 0.08). Flights of stairs climbed each day (P_{trend} = 0.58) and heart rate (P_{trend} = 0.27) were both not associated with lung cancer risk. Although power was limited to detect a difference, these associations between physical activity measures and lung cancer did not seem to differ strongly according to sex, age, body mass index, smoking status, or pack-years smoked. Reductions in lung cancer risk were observed with increasing total physical activity index scores in both current and never/former smokers, although the risk reduction was somewhat stronger and statistically significant only in current smokers (Table 3; $P_{interaction}$ = 0.99). Similarly, lung cancer risk appeared to decline with increasing total physical activity index scores among both men and women, although the risk reduction was stronger and statistically significant only in men (Table 3; $P_{interaction}$ = 0.55). The mean WBC count for lung cancer cases was significantly higher at baseline (mean, 8.2 $\times 10^3/\mu L$; SD, 2.2 $\times 10^3/\mu L$) than for participants who did not develop lung cancer (mean, 7.4 $\times 10^3/\mu L$; SD, 2.1 $\times 10^3/\mu L$; $P < 0.0001$). After multivariable adjustment, the HR for lung cancer was 2.8 times as high in participants with WBC counts ≥8 $\times 10^3/\mu L$ compared with those having counts <6.4 $\times 10^3/\mu L$ (Table 2; Fig. 1B). The mean levels of albumin at baseline among the lung cancer cases were essentially the same (mean, 4.6 g/dL; SD, 0.4 g/dL) as for noncases (mean, 4.7 g/dL; SD, 0.4 g/dL; P = 0.17), and no association was observed after multivariable adjustment.

The variables in Table 2 were similarly associated with lung cancer incidence and lung cancer mortality (data not shown), although for WBC count the relation was somewhat stronger for lung cancer mortality (HR, 3.75; 95% CI, 1.89-7.42 for tertile 3 versus tertile 1).

The results shown in Table 2 were negligibly affected by further adjustment for the presence of diabetes and emphysema at baseline (data not shown). Similarly, the further exclusion of 7 cases diagnosed between 12 and 24 months after the baseline examination had a negligible effect on the results. The relations among lung cancer risk, physical activity, and WBC count did not seem to be modified by time since the baseline examination. In analyses stratified by the median time between baseline exam and diagnosis (7.9 years), lung cancer risk was associated with physical activity and WBC count for both time frames (data not shown). There was limited power to examine these relations by histologic subtype. Compared with subjects in the lowest total physical activity index tertile, subjects in the highest tertile were 0.73 (95%

CI, 0.40-1.31) times as likely to develop any non–small cell lung cancer and 0.95 (95% CI, 0.41-2.21) times as likely to develop adenocarcinoma. Subjects in the highest tertile of WBC count were 3.04 (95% CI, 1.31-7.07) times more likely to develop non–small cell lung cancer and 2.42 (95% CI, 0.89-6.82) times more likely to develop adenocarcinoma than those in the lowest tertile. Too few cases were available to evaluate other specific cell types according to physical activity or WBC count.

To assess whether the inverse association between physical activity and lung cancer risk was mediated by inflammation, the regression models evaluating the physical activity/lung cancer association were additionally adjusted for WBC count at baseline (Table 2, second column of HR). This adjustment led to very minimal changes in the lung cancer HRs associated with the various measures of physical activity. Similarly, the lung cancer HRs associated with WBC count were not substantially changed after additionally adjusting for total physical activity index (HR, 2.76; 95% CI, 1.54-4.95 and HR, 2.76; 95% CI,1.55-4.91, for 6.4-7.9 $\times 10^3/\mu L$ and $\geq 8 \times 10^3/\mu L$ versus $<6.4 \times 10^3/\mu L$, respectively). Finally, WBC count did not seem to modify the relation between total physical activity index and lung cancer risk ($P_{interaction} = 0.86$).

Discussion

In this study, we found an inverse association between physical activity and lung cancer risk. We also found evidence for a positive association between lung cancer risk and WBC count, but not serum albumin. It has been hypothesized that physical activity may lower lung cancer risk by reducing chronic inflammation. We found no evidence, however, that the associations of physical activity and WBC count with lung cancer risk were mediated through the same biological pathway.

Clearly smoking is a strong causal factor of lung cancer in both men and women, with a population attributable risk of approximately 75% to 90% in the United States (39, 40). Smoking prevention and cessation are the primary prevention strategies needed to reduce lung cancer incidence. However, the elucidation of other risk factors would aid in lung cancer prevention, particularly in never and former smokers, in whom ~50% of all new lung cancers are diagnosed (41). This study adds additional evidence to the body of literature that suggests that physical activity is a protective factor against the development of lung cancer.

We observed an inverse association between physical activity and lung cancer at the upper end of the 10% to 40% range of risk reductions observed in the majority of past studies (14). Given the strong relation between smoking and lung cancer risk, residual confounding of the relation between lung cancer risk and both physical activity and WBC count remains a concern. In models adjusted for sex, body mass index, alcohol, and education, but not smoking, the relations between lung cancer and physical activity and WBC count were stronger (HR, 0.43 and HR, 5.05 for third tertile versus first tertile of total physical activity index and WBC count, respectively) than in models fully adjusted for smoking (HR, 0.55 and HR, 2.81, respectively). Thus, it is possible that better measurement of smoking (e.g., more accurate reporting, biomarkers of smoking history) would further attenuate our findings. However, we were able to adjust for a number of prospectively obtained self-reported smoking parameters, including smoking status, amount of smoking (pack-years), and time since smoking cessation. In analyses stratified by smoking status, physical activity seemed to be associated with reduced lung cancer risk among never and former smokers combined, although this did not reach statistical significance. Too few cases were observed among never smokers ($n = 16$) to examine this stratum separately. The relation between smoking and adenocarcinoma is weaker than for other cell types (42). In our data, adenocarcinoma was associated with WBC count but not total physical activity index score. Although this was based on only 31 events, it suggests additional caution in interpreting the physical activity/lung cancer association.

Exercise is associated with reduced systemic inflammation (particularly C-reactive protein) both between persons in cross-sectional studies and within persons after the initiation of training regimens (21). Inflammation has been proposed to promote carcinogenesis in a wide spectrum of cancers, including lung, through its effects on cell proliferation, survival, and migration (24-26). Inflammatory lung conditions, such as chronic bronchitis and asthma, have previously been linked with increased lung cancer risk (43). Furthermore, the use of aspirin and other nonsteroidal anti-inflammatory drugs has been associated with reduced lung cancer risk (44, 45).

We investigated the relation between two inflammatory markers and lung cancer. WBC count is a widely used nonspecific marker of systemic inflammation (26, 46, 47). We observed reduced WBC counts in participants who reported higher physical activity levels, consistent with previous findings (19, 23, 48). Notably, we found that this relation persisted after adjustment for self-reported smoking history. Three studies have reported positive associations between WBC count and lung cancer incidence or mortality after adjustment for smoking (30, 46, 47). Similar to our study, Shankar et al. (46) reported increased lung cancer mortality among subjects in the upper quartile of WBC count compared with those in the lowest quartile (risk ratio, 2.58; 95% CI, 0.72-9.26 for quartile 4 versus quartile 1). The results from our study (incidence HR, 2.81; 95% CI, 1.58-5.01, and mortality HR, 3.75; 95% CI, 1.89-7.42) and Shankar et al. (46) provide greater risk estimates than those for quartile 4 versus quartile 1 of WBC count in Erlinger et al. (ref. 47; mortality HR, 1.79; 95% CI, 0.88-3.62) and the recently reported results of the Women's Health Initiative (ref. 30; incidence HR, 1.63; 95% CI, 1.35-1.97). The Women's Health Initiative observed little difference between lung cancer incidence and mortality HRs in relation to WBC count.

Serum albumin is a negative acute phase protein: its concentration in the blood is reduced in response to inflammation (49, 50). At least one study has reported an approximate 25% reduction in cancer mortality among middle-aged men with a 1 SD increase in serum albumin (51). We observed little difference in serum albumin among participants according to physical activity level, and no association between serum albumin and lung cancer risk.

To investigate the hypothesis that physical activity lowers lung cancer risk by decreasing systemic inflammation, we further adjusted the regression model of physical activity and lung cancer risk for WBC count. In an adequately adjusted model, one would expect the association between physical activity and lung cancer risk to be attenuated if the relation was mediated at least in part by inflammation (represented by WBC count; ref. 52). However, we found that the associations between lung cancer risk and both physical activity and WBC count were practically unchanged after simultaneous adjustment. Thus, the effect of physical activity on lung cancer risk does not seem to be mediated by inflammation, as represented by WBC count. Importantly, WBC count is only one marker of inflammation; it remains possible that other measures of inflammation may be more relevant to the relation of physical activity and lung cancer.

Physical activity has been proposed to lower lung cancer risk by a variety of other mechanisms. Physical activity might reduce the concentration of carcinogenic agents in the airways, the duration of agent-airway interaction, and particle deposition through increased ventilation and perfusion (53). Physical activity also reduces insulin-like growth factor levels that stimulate cell proliferation (54). Furthermore, physical activity may enhance immune function or endogenous antioxidant defenses (17, 55, 56).

A number of limitations must be considered in the interpretation of this study. We used a simple assessment of physical activity. Although an increased heart rate is an objective measure associated with lack of physical activity (57, 58), heart rate is also modified by general health, stress, and other psychosocial factors. Questions regarding the number of blocks walked per week and flights of stairs climbed per day have previously been used in combination with data on recreational physical activity to measure the relation between physical activity and cancer risk in the Harvard Alumni Health Study (5, 6, 59). We did not collect data on specific participation in recreational physical activities, but rather episodes of sweat-inducing activities. A moderate correlation (r = 0.54-0.62) has been reported between episodes of sweat-inducing activities and the Harvard Alumni Activity Survey scores (60, 61), including one study in a population of older women (62). The association between sweat-inducing activities and physical fitness measured on a cycle ergometer, however, has been reported to be stronger in men (r = 0.46) than in women (r = 0.26; ref. 60). Our summary physical activity measure that combined blocks walked, stairs climbed, and sweat-inducing activities was more strongly related to lung cancer risk among men than in women (Table 3), although the test for effect modification did not reach statistical significance ($P_{\text{interaction}}$ = 0.46).

The limited scope of our physical activity assessment failed to capture variation in the intensity and duration of sweat-inducing activities. To create our total physical activity index, we assumed a typical duration of 30 minutes for sweat-inducing activities, with an intensity level equivalent to jogging (multiple of resting metabolic rate = 7). The results did not seem sensitive to variation in these assumptions: assuming a multiple of resting metabolic rate of 5 for 30 minutes or a multiple of resting metabolic rate of 9 for 1 hour for sweat-inducing activities, both resulted in a HR of 0.55 for the third tertile of total physical activity index compared with the first tertile.

Notably, our physical activity assessment also failed to capture past history of physical activity. Our failure to capture variation in duration, intensity, and past history of activity would be expected to attenuate the reductions in risk observed in our study. Much more sophisticated assessments of physical activity have been developed since the initiation of our study. Further studies are necessary, in particular, to evaluate lung cancer risk in relation to cumulative lifetime physical activity and to discriminate the effects of physical activity during different time periods in life.

Other unmeasured aspects of a healthy lifestyle may confound the relation between physical activity and lung cancer. A diet high in fruits and vegetables has been associated with reduced lung cancer risk (63). Unfortunately, we had limited information on diet and were unable to control for this in our analysis.

The strengths of this study included a population-based cohort of both sexes with excellent follow-up, the prospective assessment of physical activity and inflammatory markers, and the ability to control for a number of prospectively obtained smoking parameters. It is possible that lower levels of physical activity among future cases might be expected at the baseline exam due to symptoms related to undiagnosed lung cancer, such as pain or fatigue. To reduce the potential for this bias, we excluded all lung cancer cases who were diagnosed within 12 months of the baseline examination (n = 13). Other diseases, particularly of the lung, may also influence physical activity, inflammation, and lung cancer risk. However, we observed little change in the relations among lung cancer risk, physical activity, and WBC count after adjusting for self-reported emphysema and diabetes.

Lung cancer is both the most common cancer diagnosis in the world and the most common cause of death from cancer (64). The global burden of smoking-related disease is overwhelming, with over 1.3 million new cases of lung cancer and approximately 1.2 million deaths in 2002 (64). Smoking prevention and cessation are imperative in reducing the mortality associated with this disease. Continued study of physical activity in relation to lung cancer risk, particularly among never smokers, may further our understanding of this disease and reveal additional strategies for reducing its burden.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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