The Association of Physical Activity with Lung Cancer Incidence in a Cohort of Older Women: The Iowa Women's Health Study

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Abstract

Background: **We examined the potential association between physical activity and lung cancer in women.**
Methods: **In 1986, 36,929 women from Iowa, who were free of prior cancer, completed a questionnaire regarding physical activity, smoking, body mass index, and other life-style factors. Women were followed through 2002 for cancer incidence.**
Results: **After adjusting for potential confounders, women with high physical activity levels were less likely [hazard ratio, 0.77; 95% confidence intervals (CI), 0.64-0.94] to develop lung cancer than women with low activity levels. This hazard ratio was 0.72 (95% CI, 0.55-0.94) in current smokers and 0.63 (95% CI, 0.43-0.92) in former smokers, but was not significant in never smokers.**
Conclusion: **These results suggest that physical activity might reduce the risk of lung cancer in women who are current or former smokers.** (Cancer Epidemiol Biomarkers Prev 2006;15(12):2359–63)

Introduction

Lung cancer is the second most commonly diagnosed cancer among men and women in the U.S. and the incidence rate increases with age (1). Because lung cancer has a high incidence rate and a low survival rate, it is important to study the risk factors that may help prevent the disease from developing. It has been well established that cigarette smoking is the most important risk factor for lung cancer (2). Indeed, it has been speculated that ~80% to 90% of lung cancers in the U.S. may be attributed to cigarette smoking (3). Nonetheless, it is likely that there are other modifiable risk factors, in addition to avoiding active and passive smoking, which would assist in the prevention of lung cancer. Furthermore, given that many smokers never develop lung cancer, it is possible that there are additional factors which may diminish or exacerbate the risk associated with smoking.

There are several plausible mechanisms by which physical activity may reduce the risk of lung cancer (4-8). For example, physical activity improves pulmonary function, which may reduce the concentration of carcinogenic agents in the airway, reduce the duration of agent-airway interaction, and reduce the extent to which carcinogenic particles are deposited into the airways (5-8). Although plausible mechanisms exist, evidence regarding the association between physical activity and lung cancer has been conflicting; seven studies have shown an inverse association (5-11), whereas eight others have reported no association (12-19). The present analysis uses data from the Iowa Women's Health Study to analyze the association of physical activity with lung cancer incidence in a cohort of older women.

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Materials and Methods

Study Design and Follow-up. In 1986, ~100,000 women between the ages of 55 and 69 years with a valid (1985) Iowa driver's license were randomly selected and mailed questionnaires. The 41,836 (42%) women who returned the questionnaire were subsequently followed for mortality and cancer incidence. When participants were compared with nonparticipants, they were on average 2 months younger and were more likely to live in rural areas (20). The University of Minnesota's Institutional Review Board approved this research study.

Follow-up questionnaires were sent out in 1987, 1989, 1992, and 1997 to update vital status. In addition, deaths were identified through an annual computer linkage between participant identifiers and Iowa death certificates, and through the National Death Index for participants who did not respond to follow-up questionnaires or who had moved from Iowa. The response rates among participants for the four follow-up questionnaires, among those alive when the questionnaire was mailed, were 91%, 89%, 83%, and 79%, respectively.

Cancer occurrences were ascertained through the State Health Registry of Iowa, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program. From January 1, 1986 to December 31, 2002, 952 women were diagnosed with lung cancer. Participants with a history of cancer at baseline other than non–melanoma skin cancer were excluded (n = 3,830). Also, subjects with missing physical activity information at baseline were excluded (n = 1,077). Lastly, subjects with missing smoking information at baseline were excluded (n = 519). After these exclusions, 36,410 participants, including 777 who developed lung cancer, were included in this analysis.

Baseline Exposure Assessment. Physical activity level at baseline was established through three questions. The first question, used by the Gallup Poll (21), asked ''Aside from any work you do at home or at a job, do you do anything regularly—that is on a daily basis—that helps you keep physically fit?'' This question was used to determine whether or not participants were involved in regular physical activity. Participants were then asked ''How often, in your free time, do you take part in moderate physical activity (such as bowling, golf, light sports or physical exercise, gardening, taking long

walks)?'' and ''How often, in your free time, do you take part in vigorous physical activity (such as jogging, racquet sports, swimming, aerobics, strenuous sports)?'' Response options for these two questions included; more than four times a week, two to four times a week, about once a week, a few times a month, a few times a year, and rarely or never. Three levels of physical activity were derived from these two questions. Women were given a ''high'' physical activity level score if they participated in vigorous activity two or more times a week or participated in moderate activity more than four times per week. Women were given a ''medium'' physical activity level score if they participated in vigorous activity once a week or participated in moderate activity one to four times a week. All remaining women were given a ''low'' physical activity level score. There is evidence that the derived physical activity level variable has predictive validity for coronary heart disease incidence (22, 23).

Information regarding smoking history was also collected at baseline. Women were asked whether or not they had smoked >100 cigarettes in their entire life. Those who reported smoking >100 cigarettes in their life were asked a variety of smoking-related questions to assess current smoking status, duration of smoking, and number of cigarettes smoked per day. Using responses to these questions, women were classified as never, former, or current smokers. Also, a variable representing pack-years of smoking was calculated as the product of the average number of packs per day and the number of years smoked.

Demographic information regarding age, education, and marital status was collected via self-report. Finally, participants filled out an adapted Willett food frequency questionnaire to assess dietary habits. The validity of this questionnaire was evaluated in this population (24). Intakes of a variety of foods and nutrients were calculated from the food frequency questionnaire including alcohol, coffee, vegetables, fat, and energy. Reported body weight and height were used to calculate body mass index (BMI; in kg/m^2).

Statistical Analysis. Baseline characteristics of physically active and nonactive participants were compared using Pearson's χ^2 test for categorical variables and the t test for continuous variables. Age-adjusted and multivariate-adjusted hazard ratios (HR) and confidence intervals (CI) were computed using Cox proportional hazards regression with the SAS procedure PHREG (25). Separate models were computed for the following four physical activity measures: engagement in regular physical activity (yes, no), level of physical activity (low, medium, high), moderate activity level (never, less than once a week, more than once a week), and vigorous activity level (never, less than once a week, more than once a week). Also, separate models were conducted to examine the association between physical activity and each histologic type of lung cancer. To examine possible differences in the association between physical activity and lung cancer in accord with smoking status, analyses were stratified by smoking status (current, former, never), and pack-years of smoking (1-19 years, 20 or more years).

Variables evaluated for potential confounding are those displayed in Table 1. BMI, smoking status, pack-years of smoking, education, marital status, alcohol intake, coffee intake, and vegetable intake met our confounding criteria ($P < 0.05$ for univariate associations with both physical activity and lung cancer) and were therefore included in the multivariate models.

Results

Descriptive Data. Compared with women who were physically active, women with a low physical activity level at baseline were more likely to smoke, were less likely to have a high school education, and were more likely to be obese. They were also less likely to drink coffee and alcohol and they consumed fewer servings of vegetables each week (Table 1). Although there were statistically significant differences in other baseline characteristics across activity levels, the magnitudes of these differences were trivial.

Table 1. Baseline characteristics of participants by physical activity level (The Iowa Women's Health Study, 1986)

Characteristic	Physical activity level		
	Low (%)	Medium (%)	High (%)
Mean age, years (SD)	61.5 (4.2)	61.7 (4.2)	61.8 (4.2)
Smoking status			
Current	19	13	10
Former	18	19	22
Never	63	69	68
Pack-years of smoking			
0	63	69	69
1-19	13	14	15
20-39	13	11	10
≥40	11	7	7
Education level			
Less than high school graduate	22	17	16
High school graduate	44	42	39
More than high school	35	42	46
Marital status			
Never married	2	3	2
Currently married	76	77	79
Separated/divorced	5	4	4
Widowed	17	16	15
BMI categories			
<25	35	41	46
25-29	36	38	37
≥30	29	20	16
Diabetes			
Yes	7	5	5
No	93	95	95
Alcohol categories (g/d)			
0	59	53	54
≤4	22	26	25
>4	19	22	21
Coffee categories			
Never or rarely	61	56	56
1-3 cups/mo	11	12	11
<1 cup/d	14	18	18
≥1 cups/d	14	15	15
Energy intake tertiles (kcal/d)			
<1,473.2	35	32	32
1,473.2-1,955.4	32	35	34
>1,955.4	33	34	34
Vegetable intake tertiles (servings/wk)			
<18	39	30	24
18-28	32	35	34
>28	28	36	42
Fat intake tertiles (g/d)			
<53.4	33	32	36
53.4-75.0	32	35	34
>75.0	35	33	31

NOTE: All χ^2 tests yielded $P < 0.01$.

Over 546,294 person-years of follow-up, 777 women were diagnosed with lung cancer: 125 nonsmokers, 177 former smokers, and 475 current smokers. The lung cancers were 38% adenocarcinomas, 19% squamous cell, 19% small cell, and 24% other types. Compared with never smokers, current, and former smokers had proportionally more squamous cell and small cell subtypes (14% versus 45% versus 33%, respectively).

Association Between Physical Activity and Lung Cancer. There was a significant inverse association between physical activity and lung cancer after adjusting for potential confounders including cigarette smoking status and pack-years of smoking (Table 2). Women who had a high physical activity level were 23% (HR, 0.77; 95% CI, 0.64-0.94) less likely to be diagnosed with lung cancer as women who had a low physical

Table 2. HR of lung cancer associated with different measures of leisure physical activity, each measure's association estimated from a separate proportional hazards model (The Iowa Women's Health Study, 1986-2002)

Physical activity variable	Cases	Person-years	Age-adjusted HR	Multivariate-adjusted HR*
Regular physical activity				
No	526	318,111	1.00 (ref)	1.00 (ref)
Yes	251	228,182	0.66 (0.57-0.77)	0.92 (0.79-1.07)
Physical activity level				
Low	461	255,853	1.00 (ref)	1.00 (ref)
Medium	176	152,020	0.64 (0.54-0.76)	0.84 (0.70-1.00)
High	140	138,421	0.56 (0.46-0.67)	0.77 (0.64-0.94)
Moderate physical activity				
Never	235	109,658	1.00 (ref)	1.00 (ref)
≤1/wk	234	155,351	0.70 (0.58-0.84)	0.90 (0.75-1.09)
>1/wk	308	281,285	0.51 (0.43-0.60)	0.79 (0.66-0.94)
Vigorous physical activity				
Never	691	451,485	1.00 (ref)	1.00 (ref)
≤1/wk	48	48,215	0.65 (0.49-0.87)	0.80 (0.60-1.07)
>1/wk	38	46,593	0.54 (0.39-0.74)	0.71 (0.51-0.99)

*Adjusted for baseline age, BMI (<25, 25-30, >30), smoking (current, former, never), pack-years of smoking (0, 1-19, 20-39, 40+), education (less than high school, high school graduate, more than high school), marital status (married, not married), alcohol intake (0, ≤4, >4 g/d), vegetable intake (<18, 18-28, >28 servings/wk).

activity level. Women who participated in moderate activity more than once a week were 21% (HR, 0.79; 95% CI, 0.66-0.94) less likely to develop lung cancer as women who never participated in moderate physical activity. Finally, women who participated in vigorous activity more than once a week were 29% (HR, 0.71; 95% CI, 0.51-0.99) less likely to have lung cancer compared with women who rarely or never participated in vigorous activity.

Results from analyses examining the association of physical activity by histologic subtype of lung cancer are presented in Table 3. In the age-adjusted models, women who had a high physical activity level were less likely to have each of the four subtypes considered compared with women with a low activity level. In multivariate-adjusted analyses, the risk estimates were attenuated and no longer statistically significant (except for subtype other/not otherwise specified).

Analyses Stratified by Smoking Status. Results from analyses stratified by smoking status are presented in Table 4. The incidence rates illustrate the powerful effect of smoking on lung cancer and the more modest rate association of physical activity with lung cancer occurrence. Among women who were current smokers, a moderate physical activity level was associated with a 0.65-fold (95% CI, 0.51-0.83) lower risk of developing lung cancer compared with a low physical activity level, and a high physical activity level was associated with a 0.72-fold (95% CI, 0.55-0.94) lower risk. Former smokers who had moderate or high activity levels were also at a lower risk of developing lung cancer (Table 4). Among never smokers, there was no monotonic association between activity level and lung cancer incidence, with the incidence elevated in the moderate physical activity category only (HR, 1.83; 95% CI, 1.21-2.78). Nevertheless, the smoking status by physical activity multiplicative interaction was not statistically significant.

A secondary analysis was done, excluding cases that occurred during the first 2 years of follow-up (n = 70). The HRs for Tables 2–4 did not change appreciably (data not shown).

Discussion

This Iowa Women's Health Study analysis suggests that independent of smoking status, pack-years of smoking, and other confounders, physical activity is associated with a decreased risk of lung cancer in women, and both moderate and vigorous physical activity were associated with risk reductions. Physical activity had a moderate inverse association with risk of lung cancer in current and former smokers.

Comparison with Previous Research. Many studies have examined the association between physical activity and lung cancer risk (5-19) but most of these studies included only men (7, 8, 10-12, 14, 15, 17, 19). Of the six studies that examined this association in women, three reported independent inverse associations between physical activity and lung cancer risk (5, 6, 9), whereas the other three reported no association in women (13, 16, 18). Two of the prior null studies were limited

Table 3. HR of lung cancer associated with leisure physical activity by histologic subtype (The Iowa Women's Health Study, 1986-2002)

Histologic subtype	Physical activity level	Cases	Person-years	Age-adjusted HR	Multivariate-adjusted HR*
Squamous cell carcinoma	Low	85	25,264	1.00 (ref)	1.00 (ref)
	Medium	36	150,805	0.71 (0.48-1.04)	1.01 (0.68-1.50)
	High	23	137,288	0.49 (0.31-0.78)	0.77 (0.48-1.24)
Adenocarcinoma	Low	159	253,195	1.00 (ref)	1.00 (ref)
	Medium	77	151,179	0.81 (0.62-1.07)	0.95 (0.72-1.26)
	High	63	137,697	0.73 (0.55-0.98)	0.86 (0.64-1.16)
Small cell carcinoma	Low	96	252,613	1.00 (ref)	1.00 (ref)
	Medium	26	150,650	0.46 (0.30-0.71)	0.70 (0.45-1.08)
	High	25	137,326	0.48 (0.31-0.75)	0.91 (0.58-1.43)
Other/not otherwise specified	Low	121	252,990	1.00 (ref)	1.00 (ref)
	Medium	37	150,872	0.50 (0.34-0.72)	0.63 (0.44-0.92)
	High	29	137,391	0.42 (0.28-0.64)	0.56 (0.37-0.85)

*Adjusted for baseline age, BMI (<25, 25-30, >30), smoking (current, former, never), pack-years of smoking (0, 1-19, 20-39, 40+), education (less than high school, high school graduate, more than high school), marital status (married, not married), alcohol intake (0, ≤4, >4 g/d), vegetable intake (<18, 18-28, >28 servings/wk).

Table 4. HR of lung cancer associated with leisure activity by smoking status or BMI (The Iowa Women's Health Study, 1986-2002)

Smoking status	Physical activity level	Cases	Person-years	Crude incidence rate per 10^4	Age-adjusted HR	Multivariate-adjusted HR*
Current smokers	Low	324	44,634	72	1.00 (ref)	1.00 (ref)
	Medium	84	17,519	48	0.65 (0.51-0.82)	0.65 (0.51-0.83)
	High	67	12,807	52	0.70 (0.54-0.91)	0.72 (0.55-0.94)
Former smokers	Low	95	45,734	21	1.00 (ref)	1.00 (ref)
	Medium	42	27,886	15	0.72 (0.50-1.04)	0.72 (0.50-1.04)
	High	40	29,557	14	0.65 (0.45-0.94)	0.63 (0.43-0.92)
Never smokers	Low	42	165,485	3	1.00 (ref)	1.00 (ref)
	Medium	50	106,615	4	1.82 (1.21-2.74)	1.83 (1.21-2.78)
	High	33	96,056	3	1.33 (0.84-2.10)	1.32 (0.83-2.10)

*All HRs adjusted for baseline age, education (less than high school, high school graduate, more than high school), marital status (married, not married), alcohol intake (0, ≤4, >4 g/d), vegetable intake (<18, 18-28, >28 servings/wk). HRs within smoking groups also adjusted for BMI (<25, 25-30, >30).

with regard to the number of lung cancer cases, with only 51 and 59 cases in women, respectively (13, 16). The third null study used occupational title as a surrogate measure of physical activity (18).

Three studies have reported similar findings to our study. Mao et al. completed a population-based case-control study with 997 female cases and 1,464 female controls. They reported that women with a high activity level were 0.72-fold less likely to develop lung cancer than women with a low activity level. They also reported that women who were ex-smokers or current smokers and had high activity levels were less likely to develop lung cancer than ex-smokers or current smokers with low activity levels but there was no association between activity level and lung cancer risk for women who had never smoked. Again similar to our study, Mao et al. reported that women with a low or moderate BMI who were highly active were less likely to develop lung cancer than women with a low or moderate BMI who had a low activity level, after controlling for smoking status (6). There was no association between activity and lung cancer incidence for women with a high BMI.

Kubik et al.'s case-control study had 419 cases, including 130 nonsmoking (never smokers and those who quit >20 years ago) cases, and 1,593 controls. They reported that among women who smoked, those with >6 h/wk of physical exercise were 0.48-fold less likely to develop lung cancer than those with 0 to 2 h of activity per week. Similar to our results, Kubik et al. observed that this reduction in risk was not apparent among nonsmokers (5).

Finally, Alfano et al. completed a study, drawn from the β-Carotene and Retinol Efficacy Trial, examining physical activity and lung cancer incidence and mortality among 2,878 female current or former smokers. They reported no association between physical activity and lung cancer incidence. However, women who were physically active were at a decreased risk of lung cancer mortality compared with women who were not physically active (9).

Contrary to our findings, Mao et al. observed that the inverse association between physical activity and lung cancer varied by histologic subtype, such that women with squamous cell and small cell carcinomas experienced the greatest risk reduction. It is possible that the difference in study results is due to the small sample sizes when lung cancers were broken down into histologic subtypes in our cohort. Despite the lack of heterogeneity of physical activity associations across subtype in our study, the age-adjusted HRs comparing high to low activity levels were somewhat lower for squamous cell and small cell carcinomas. On the other hand, these differences disappeared once the models were adjusted for potential confounders.

Potential Mechanisms. If physical activity does reduce the risk of lung cancer, it is likely due to training-induced alterations in the physiologic response to smoking or environmental exposures associated with the development of lung cancer. For example, it has long been observed that immunocompromised individuals are at a higher risk for lung cancer (26), and moderate intensity exercise training has been shown to improve immune function (27). Smoking and environmental respiratory exposures also result in inflammatory responses (28), and exercise training has been shown to attenuate these same responses (29-34). Finally, there certainly is evidence for increased oxidative stress due to both smoking and environmental exposures (28), and exercise training has been observed to increase endogenous free radical scavengers, even in smokers (35). Perhaps exercise training may be thought of as an incremental and controlled physiologic stress that enables the body to respond to smoking and environmental stresses more effectively.

Strengths and Weaknesses. There are several strengths to our study. First, we have a large cohort study of women who have been followed for almost 20 years. Most previous research on physical activity and lung cancer involved only men. Also, because of the cohort design of our study, we were able to study physical activity and smoking well before the women developed lung cancer. We were also able to control for many potential confounding variables that other studies did not address.

Despite the many strengths of our study, there are also a few limitations. First, there is potential for residual confounding. That is, it is possible that smokers who are active tend to smoke less, inhale less, use less risky cigarettes, or otherwise lead healthier life-styles than those who are inactive. The fact that the association between physical activity and lung cancer was nonexistent in never smokers in this and other studies further suggests that residual confounding may be a problem. On the other hand, it is possible that there are effect modifications such that physical activity only ''protects'' against lung cancer in the setting of cigarette smoke exposure. Second, physical activity was only measured once, and the questions used have not been validated against physiologic variables. The questions have, however, been shown to have predictive validity in coronary heart disease incidence (22, 23). Lastly, despite being a large study, sample size was limited for some subgroup analyses.

Summary. Our study provides evidence that physical activity may reduce the risk of lung cancer in women, particularly among current and former smokers. It is important that these results not be interpreted as an endorsement of smoking for those who are physically active. As shown by the incidence rates presented in Table 4, the absolute risk of lung cancer is still much greater in current and former smokers, regardless of activity level, than in never smokers. Quitting smoking is the single most important action a smoker can take to reduce risk of lung cancer.

The knowledge that physical activity may reduce the risk of lung cancer incidence among women smokers may be useful in the context of harm reduction among smokers not currently willing to attempt smoking cessation or who have recently failed a quit attempt. Furthermore, there is some evidence that exercise may be an efficacious intervention to assist women smokers who are concerned about weight gain during the process of quitting (36). Future research should examine whether the association is causal. Animal models of lung cancer might be able to test the physical activity hypothesis experimentally. If potentially causal, examination of mechanisms for this apparent risk reduction would be helpful (e.g., whether exercise among women smokers would alter smoking patterns or physiologic response to smoking in a manner that would reduce harm). To reiterate, however, even if there were a significant reduction of risk among women who are heavy smokers and who are physically active, quitting smoking is unarguably the most important action for the reduction of lung cancer risk.

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