Physical Activity in Relation to All-Site and Lung Cancer Incidence and Mortality in Current and Former Smokers

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Abstract

Increased physical activity has been associated with a reduction in the incidence and mortality from all-site cancer and some site-specific cancers in samples of primarily nonsmoking individuals; however, little is known about whether physical activity is associated with similar risk reductions among smokers and ex-smokers. This study examined physical activity in relation to all-site cancer and lung cancer incidence and mortality in a sample of current and former smokers (*n* = 7,045; 59% male; 95% Caucasian; mean age, 63 years) drawn from the β-Carotene and Retinol Efficacy Trial, a lung cancer chemoprevention trial. Hazard rate ratios and 95% confidence intervals associated with a 1 SD increase in physical activity were 0.86 (0.80-0.94) for all-site cancer only among men, 0.84 (0.69-1.03) for lung cancer only for younger participants, 0.75 (0.59-0.94) for cancer mortality among younger participants and 0.68 (0.53-0.89) among women, and 0.69 (0.53-0.90) for lung cancer mortality only among women. These results suggest that incidence may be more attenuated by physical activity for men and mortality more attenuated for women. Effects may be more pronounced for younger people and may differ inconsistently by pack-years of smoking. Physical activity may play a role in reducing cancer risk and mortality among those with significant tobacco exposure. Prospective studies using more sophisticated measures of physical activity assessed at multiple time points during follow-up are needed to corroborate these associations. (Cancer Epidemiol Biomarkers Prev 2004;13(12):2233–41)

Introduction

It is crucial to understand how modifiable risk factors can influence cancer incidence and mortality because two thirds of cancers could be prevented through lifestyle modification (1-3). Among people who smoke, physical activity may be one such factor that could be employed together with smoking cessation to reduce cancer morbidity and mortality. Four reviews of the literature suggest that physical activity seems to decrease risk (4-7) and mortality (4, 5) from all-site cancer in both men and women. Risk reduction estimates vary in the literature from 46% (7) to 81% (8). However, most research has been conducted with populations of primarily nonsmoking individuals and little is known about how physical activity may affect risk of cancer morbidity and mortality in smokers and ex-smokers.

There is some evidence of an association between physical activity and lung cancer etiology (9). Several studies suggest that physical activity is associated with decreased risk of lung cancer in men and women, after adjusting for smoking (10-21), with risk reduction estimates from 18% (16) to 62% (12). However, the proportions of smokers in these studies were low and the results may not be generalizable to all smokers. The only study conducted with a cohort of smokers included only males and found no association between occupational or leisure time physical activity and lung cancer risk, except for a modest risk reduction among younger smokers (11).

It is also unclear if the level of tobacco exposure modifies the association between physical activity and cancer. Three studies that evaluated this interaction with regard to colon and rectal cancers (22, 23) and lung cancer (11) found no significant interaction between smoking and physical activity. However, other studies found physical activity to be protective against lung cancer among heavier smokers but not among lighter smokers (15, 20) or nonsmokers (16).

Two reviews of the literature on physical activity and cancer conclude that it is not clear what frequency, duration, intensity, type of activity, or pattern of life span involvement in physical activity are most protective against cancers (5, 24). It is also not clear whether the relationship between physical activity and cancer follows a dose-response or a threshold pattern. A meta-analysis by Shephard and Futcher (7) concluded that much of the benefit of physical activity for all-site cancer risk was seen in moderate exercise versus sedentary

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behavior. In contrast, two recent reviews found evidence of a dose-response relationship for all-site cancer (24) and several specific cancers (9, 24).

Very few studies have evaluated the relationship between physical activity and cancer in smokers, and little is known about what intensity and amount of physical activity are important for cancer outcomes. The aim of our study was to more clearly elucidate the relationships between physical activity and both all-site cancer and lung cancer incidence and mortality and the amount of time spent performing physical activity and the intensity of physical activity and all-site cancer and lung cancer incidence and mortality, including whether these relationships follow a dose-response or threshold pattern, among current and former smokers in the β-Carotene and Retinol Efficacy Trial (CARET).

Materials and Methods

Study Population. CARET was a randomized, double-masked, placebo-controlled, chemoprevention trial designed to evaluate the effects of daily supplementation of a combination of β-carotene and vitamin A on lung cancer incidence and mortality in 4,060 asbestos-exposed workers and 14,254 heavy smokers (25). Participants were recruited from six centers across the United States beginning in 1985. Written informed consent was obtained from all participants prior to their entry into the trial. All CARET activities were reviewed and approved annually by the institutional review boards at the six CARET centers. Eligibility criteria differed for the asbestos-exposed group and the group of heavy smokers. The asbestos-exposed participants were excluded from the analyses presented here due to the focus of the current study on heavy smokers. The population of smokers was recruited into CARET from health insurance rolls and managed care organizations at three of the six centers: to be eligible, the men and women had to be ages 50 to 69 years at study entry, be current smokers or have quit in the past 6 years, and have ≥20 pack-years of smoking. Participant recruitment began in 1985 and continued through 1994. The intervention phase of CARET was ended in 1996 because of an excess of lung cancer cases and mortality in the intervention group (26, 27). Participants have continued to be followed on an annual basis for cancer and mortality outcomes. Physical activity was assessed once, in 1996, which defines the baseline measurement period for the current study. The analyses presented here are based on data collected through January 2002.

In addition to the presence of physical activity data, eligibility for the current study required that the participant have no history (before 1996) of cancer other than nonmelanoma skin cancer. Of the 14,254 heavy smokers randomized into CARET, we defined a cohort of 7,045 (49%) for analysis in the current study. The majority of those lost (4,123; 57%) were not asked to complete the physical activity questionnaire because their follow-up was conducted by phone; 587 (8%) participants did not complete the follow-up visit where physical activity was measured, 162 (2%) completed the visit but did not complete a physical activity questionnaire, 894 (12%) were deceased, 717 (10%) had been diagnosed with cancers other than nonmelanoma skin cancer before physical activity was measured, 413 (6%) had dropped out of the study, and 313 (5%) were excluded due to outliers on physical activity or other variables. From this cohort of 7,045, two subsets of those diagnosed with any cancer (n = 793) and those diagnosed with lung cancer (n = 263) were defined for analysis of all-site cancer mortality and lung cancer mortality, respectively.

Cancer Outcomes. Initial reports of cancer outcomes came from participants or their next of kin, cancer registries, state boards of health, and the National Death Index. Medical records were obtained and reviewed by the CARET Endpoints Committee. We defined four outcome variables: (1) cancer incidence at any site, (2) cancer mortality among those diagnosed with cancer, (3) lung cancer incidence, and (4) lung cancer mortality among those diagnosed with lung cancer.

Physical Activity Assessment. The self-administered physical activity questionnaire was based on a single section from the Paffenbarger Physical Activity Questionnaire (28, 29) in which participants were asked to indicate average weekday and weekend day hours during the past year in five categories that were defined for participants: sleeping, vigorous activity, moderate activity, light activity, and sitting. Examples were provided for the four intensity categories. For ''vigorous physical activity,'' examples included digging in the garden, strenuous sports, jogging, chopping wood, sustained swimming, brisk walking, heavy carpentry, and bicycling on hills. Examples provided for ''moderate activity'' were housework, light sports, regular walking, golf, yard work, lawn mowing, painting, repairing, light carpentry, dancing, and bicycling on level ground. ''Light activity'' examples included office work, driving a car, strolling, personal care, and standing with little motion. Examples of ''sitting activities'' were eating, reading, deskwork, watching television, and listening to the radio. Participants estimated their activity in each category to the nearest 0.25 hour, with separate columns for usual weekday and usual weekend day. Questionnaires were reviewed with the participant by the study interviewer at the time of the in-person interview.

The total weekly hours spent in each category of physical activity were computed as (number of hours of weekday activity × 5) + (number of hours of weekend day activity × 2). The total hours spent in the ''light,'' ''moderate,'' and ''vigorous'' categories defined total weekly hours of physical activity. Hours of ''moderate'' and ''vigorous'' categories were summed to obtain hours per week of moderate to vigorous activity. The total hours spent in the ''vigorous'' category only defined hours per week of vigorous activity. The percentage of moderate to vigorous activity that was vigorous defined a fourth exposure variable, which when analyzed in concert with the other variables provides additional information on the importance of physical activity intensity.

Although the Paffenbarger questionnaire has been validated (29), the reliability and validity of these derived variables are not known. To establish the validity of these variables, we conducted analyses examining outcomes that are widely accepted to be associated with physical activity. In this sample, the correlations between physical activity variables and body mass index (BMI) were significant and negative; additionally, increasing activity on all four measures was associated with reduced risk of death from coronary heart disease, cerebrovascular causes, and cardiovascular disease, as would be expected for valid measures of physical activity (data not shown).

Potential Confounders

Demographics and Design Variables. Basic demographic information was collected via questionnaire and included education level, ethnicity, age, gender, marital status, employment, and household structure. Family history of cancer was assessed using two variables indicating the number of relatives (0-5) who had been diagnosed with lung cancer or with other cancers. Time-dependent versions of employment and marital status were calculated at each follow-up as the percentage of follow-up time the participant was unemployed/disabled or unmarried. Indicator variables identified the participant's study condition (intervention versus placebo) and field center (Seattle, Irvine, or Portland).

Health-Related Variables. All variables used in the analysis were assessed at the visit closest to or at the visit in which physical activity was assessed. Participants reported their general health in the last 3 months (excellent, very good, good, or fair) as well as previous diagnoses of several health conditions. We used the latter to define three indicator variables that may affect physical activity: (1) cardiovascular disease (angina, heart attack, heart failure, heart murmur, high blood pressure, or stroke) or diabetes, (2) arthritis or osteoporosis, and (3) asthma, chronic bronchitis, emphysema, or asbestosis. Two additional variables indicated the severity of depressive and anxious symptoms based respectively on the Center for Epidemiological Studies Depression Scale (30) and Dupuy's General Well-Being Scale (31). Depressive and anxious symptom scale scores, along with 11 other signs and symptoms of potential treatment toxicity, were categorized on the same 0 to 5 severity scale by CARET investigators, refined during the pilot phase of the study, and used throughout the study. The scales were categorized such that a symptom grade of 4+ on each scale was indicative of a potentially serious side effect and triggered the CARET symptom management protocol (32). Anxious symptom scale scores were graded as follows: 3 = grade 0, 4-9 = grade 1, 10-15 = grade 2, 16-21 = grade 3, 22-25 = grade 4, and 26-28 = grade 5. Depressive symptom scale scores were graded as follows: 10 = grade 0, 11-17 = grade 1, 18-24 = grade 2, 25-31 = grade 3, 32-36 = grade 4, and 37-40 = grade 5. BMI was computed from height and weight (kg/m^2), which were measured in the clinic. The average daily amount of fat (g/1,000 cal), servings of fruits and vegetables, and alcohol intake (g) were calculated from a food frequency questionnaire that was adapted from the National Cancer Institute/Block food frequency questionnaire (33) to be especially sensitive to fat and carotenoids. At the baseline clinic visit, participants reported pack-years of smoking and current smoking status (current versus former smoker); time-dependent smoking status was calculated at each follow-up as the percentage of follow-up time the participant was a smoker. Health data collected >16 months from the time of physical activity measurement were set to missing. For the mortality analyses based on the smaller subsets of the cohort, categories of some categorical variables were combined where necessary due to small numbers.

Data Analysis. The association between each physical activity measure and cancer outcome was investigated with Cox regression using PHREG, SAS version 8.2 (34). Follow-up time was defined differently in the analyses of cancer incidence and mortality. For analyses of cancer incidence, follow-up time was defined as time from the date of physical activity measurement to either the date of diagnosis (cases) or the date of last follow-up contact (noncases). For analyses of cancer mortality, follow-up time was defined as time from the date of cancer diagnosis to either the date of death from that cancer (deceased cases) or the date of last follow-up contact (nondeceased cases). Quadratic and cubic components assessed any nonlinear pattern in the nature of the relationships between physical activity and each outcome. Confounding was assessed by adding the potential confounder to the model; a change in the hazard rate ratio (HRR) for physical activity of >10% provided evidence of confounding (35, 36). Study condition and field center were retained in each model because they were features of the study design. All other variables were retained only if they affected the variables of interest.

Assessing effect modification of the relationships between physical activity and cancer outcomes would help shed light on potential mechanisms by which physical activity could influence cancer. Previous studies suggested the investigation of age (11), smoking history, BMI, and gender (15) as effect modifiers. Thus, we repeated these analyses, stratifying separately by pack-year history, age, BMI (each defined by median split), and gender. The stratum-specific groups were 14-27.5 and 27.6-56 kg/m^2 for BMI, 20-44 and 45-185 for pack-years, and 54-62 and 63-78 years for age.

Although results of cohort studies are often automatically stratified by gender, we were unable to analyze the results separately by gender because the resulting reduced numbers of events in each gender specifically would have had low power for testing effect modification by age, BMI, or pack-year history. We tested effect modification by gender in a similar manner to BMI, age and pack-year history, and we present stratum-specific effects and their P values where there was evidence of a statistically significant or marginal interaction ($P < 0.10$). HRRs are presented for a 1 SD change in each physical activity variable to aid in demonstration of the results.

We tested the proportional hazards assumption for the final model for each outcome by adding an interaction between physical activity and the natural log of time. To check for nonlinear patterns in the HRR over follow-up time, we also evaluated the proportional hazards assumption categorically based on quartiles of the time to event distribution for each event type (37). Where the proportional hazards assumption was violated, we split the sample by follow-up time, where appropriate, and analyzed time-specific models. Because the HRR was significantly different in the first year versus years 2 to 5 of follow-up for only 2 of the 16 analyses, we did not see any reason to globally exclude cases diagnosed early in the follow-up period.

Results

Characteristics of the Sample. As shown in Tables 1 and 2, the participants were predominantly Caucasian, educated at least at the high school level, married, employed or retired, and lived with a relative. The mean age at the time physical activity was measured (baseline for the current study) was 63 years, and there were more men than women in the study. Participants reported a mean of approximately one relative with cancer. Most participants reported their perceived health to be good, very good, or excellent, although many had been diagnosed with chronic health conditions or were experiencing significant symptoms of cardiovascular disease. Participants reported a mean of 49 pack-years of smoking. Almost half the participants reported current smoking at baseline. The average amount of time engaged in physical activities as calculated from Paffenbarger activity data was very high, especially given the characteristics of the study population. Participants reported averaging over 35 hours per week spent in activities defined by the physical activity questionnaire as ''moderate'' to ''vigorous'' and over 8 hours per week in activities defined as ''vigorous''. These extreme values are discussed in detail below.

Out of the cohort of 7,045 participants, 793 (12%) had developed cancer during the follow-up period, including 263 (3.7%) with lung cancer (Table 3). Nearly 30% (n = 236) of participants diagnosed with any cancer died during the follow-up period, and over 54% (n = 141) of participants with lung cancer died during the follow-up period. The average length of follow-up was 1,670 days (SD = 394) for the all-site cancer analysis and 1,726 days (SD = 314) for the lung cancer incidence analysis. The average time between diagnosis and death was 627 days (SD = 533) for the all-site cancer mortality analysis and 312 days (SD = 338) for the lung cancer mortality analysis. Table 3 presents the incident cancer cases by gender. Among women, the most common types of cancer diagnoses were breast and lung cancers (each ~31%). Among men, the most frequent diagnoses were lung (32%) and prostate (28%) cancers.

Table 4 presents the results of the analysis of physical activity and incidence of all-site cancer. Gender was a marginally significant effect modifier of the relationships between total physical activity and moderate to vigorous activity and cancer incidence (P = 0.07 and 0.06, respectively). Specifically among men, there was a strong inverse relation between total physical activity and cancer risk (HRR, 0.86; P = 0.0004) and a weaker inverse relation for moderate to vigorous physical activity and cancer risk (HRR, 0.93; P = 0.08). Physical activity was not associated with all-site cancer risk in women. For vigorous physical activity and percentage of moderate to vigorous activity that was vigorous, the proportional hazards assumption was violated for the models run on the entire follow-up period; thus, time-specific models are presented. In each case, physical activity was significantly associated with reduced risk of cancer in the first year of follow-up (respective HRRs, 0.68 and 0.75; P = 0.001 and 0.002) but not in years 2 to 5 of follow-up. In each of these results, there was no evidence of a nonlinear or threshold effect for measures of physical activity in any model. Thus, each of these associations represents a linear or dose-response effect.

Table 4 also presents the results of the analyses predicting lung cancer incidence. Age was a significant effect modifier of the relation between total physical activity and lung cancer risk (P = 0.04). Specifically among younger participants (ages 54-62 years), a 1 SD

Table 1. Characteristics of the study sample by incident cancers or deaths for continuous variables

	All participants (n = 7,045)		Incident cancer cases (n = 793)		Incident lung cancer cases (n = 263)		All cancer deaths (n = 236)		Lung cancer deaths (n = 141)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (y)	63.02	5.71	64.86	5.29	65.29	5.09	65.08	5.24	65.47	5.23
No. relatives with lung cancer*	0.14	0.38	0.12	0.36	0.13	0.36	0.14	0.38	0.14	0.39
No. relatives with other cancer*	0.88	1.01	0.91	1.05	0.91	1.00	0.93	1.03	0.94	1.04
Anxiety grade†	1.30	0.80	1.28	0.85	1.22	0.81	1.23	0.83	1.14	0.74
Depression grade†	0.93	0.72	0.92	0.75	0.88	0.80	0.88	0.86	0.82	0.81
BMI (kg/m^2)‡	28.09	5.18	27.77	4.95	27.15	4.68	27.56	4.70	27.11	4.57
Fat (g/1,000 cal/d)§	40.43	8.89	40.80	8.84	41.86	9.13	42.24	8.73	42.76	8.38
Alcohol (g/d)§	12.68	21.13	14.94	23.36	15.48	25.45	14.86	24.33	15.60	25.45
Fruit/vegetable (servings/d)§	3.05	1.69	2.97	1.62	2.93	1.58	2.77	1.59	2.81	1.59
Pack-years of smoking	48.62	20.01	52.87	21.29	55.86	21.17	55.47	20.04	57.76	19.91
Hours of total physical activity per week	71.43	20.03	69.49	20.27	70.40	19.09	70.06	18.12	70.90	18.32
Hours of moderate and vigorous physical activity per week	35.28	20.39	34.94	20.19	35.14	19.64	35.84	19.48	36.43	19.69
Hours of vigorous physical activity per week	8.82	11.50	8.59	11.61	8.84	11.85	9.01	12.51	9.06	12.49
% Moderate-vigorous physical activity per week as vigorous	0.22	0.21	0.21	0.22	0.22	0.22	0.21	0.22	0.22	0.22

*Familial cancer history unavailable for <1% of participants.

†Severity graded 0-5 using original scale coding from Dupuy (31) for anxiety and the CES-D (30) for depression; symptom grades missing for <1% of participants.

‡BMI missing for 1% of participants.

§Food frequency questionnaire data missing or invalid for 7% of participants.

Table 2. Characteristics of the study sample by incident cancers or deaths for categorical variables

	All participants (n = 7,045), %	Incident cancer cases (n = 793), %	Incident lung cancer cases (n = 263), %	All cancer deaths (n = 236), %	Lung cancer deaths (n = 141), %
Education*					
Some high school or less	6.26	7.19	10.27	8.47	9.22
Completed high school	20.68	17.15	16.35	20.76	17.73
Some college	38.58	37.20	34.60	37.71	38.30
College degree	11.48	11.85	11.79	9.32	9.93
Some graduate school	7.61	8.83	8.37	7.20	6.38
Graduate degree	9.17	9.21	7.98	6.78	6.38
Ethnicity					
White	95.15	96.47	96.20	97.46	97.16
Black	1.26	0.76	0.76	0.85	0.71
Hispanic	1.25	0.88	0.38	0.85	0.71
Asian/Pacific Islander	1.38	1.39	1.90	0.85	1.42
Other	0.97	0.50	0.76		
Gender					
Female	40.85	35.18	35.36	31.78	31.21
Marital status†					
Single	4.37	3.88	3.56	5.26	3.73
Married	68.33	67.18	69.17	68.42	73.13
Widowed	9.54	11.24	12.65	8.77	6.72
Divorced/separated	17.76	17.70	14.62	17.54	16.42
Employment status‡					
Employed	40.47	31.57	26.85	28.26	24.26
Homemaker	6.14	4.64	5.84	5.65	7.35
Retired	45.32	56.31	60.31	58.70	61.03
Disabled	2.20	1.93	1.56	3.04	2.21
Unemployed	2.01	1.29	1.17	0.00	0.00
Other	3.86	4.25	4.28	4.35	5.15
Household structure§					
Lives alone	19.73	20.61	23.57	22.46	22.70
Lives with relative	74.08	73.32	70.72	72.03	72.34
Lives with nonrelative	6.19	6.07	5.70	5.51	4.96
Study field center					
Seattle	40.54	41.24	44.49	42.37	44.68
Portland	29.37	31.78	30.04	35.17	34.04
Irvine	30.09	26.99	25.48	22.46	21.28
Study treatment arm					
Placebo	46.54	44.39	39.16	38.98	31.91
Active	53.46	55.61	60.84	61.02	68.09
Perceived health‖					
Excellent	14.56	15.63	16.92	15.45	18.84
Very good	40.52	38.88	36.15	36.91	34.06
Good	34.16	32.91	34.23	31.33	31.16
Fair	9.57	11.31	11.92	14.16	14.49
Poor	1.19	1.27	0.77	2.15	1.45
Cardiovascular disease factors or diabetes					
Yes	54.73	55.99	52.47	58.90	51.77
Arthritis or osteoporosis					
Yes	34.86	35.56	31.56	37.71	36.17
Asthma/chronic bronchitis or emphysema/asbestosis					
Yes	21.72	23.20	28.14	29.66	33.33
Current smoking¶					
Yes	49.69	55.27	62.69	60.09	60.14

*Education level missing for 6% of participants.
†Marital status missing for 1% of participants.
‡Employment data missing for 1% of participants.
§Household structure data missing for <1% of participants.
‖Perceived health data missing for <1% of participants.
¶Current smoking status unknown for <1% of participants.

increase in total physical activity was associated with a 16% reduced risk of lung cancer, although this effect was not statistically different from one (P = 0.09). There was no effect in the older group. There was a nonsignificant trend (P for interaction = 0.097) for the percentage of activity that was vigorous to be associated with reduced risk of lung cancer among those with fewer than 44 pack-years of smoking (HRR, 0.83; P = 0.11) but not among those with greater pack-years of smoking. These HRRs describe linear, dose-response effects; the proportional hazards assumption was consistently met.

Table 3. Incident cancer cases by gender

	All participants (793), *n* (%)	Females (279), *n* (%)	Males (514), *n* (%)
First cancer			
Bladder	47 (5.93)	8 (2.87)	39 (7.59)
Breast	88 (11.10)	88 (31.54)	—
Colorectal	48 (6.05)	16 (5.73)	32 (6.23)
Esophagus	20 (2.52)	2 (0.72)	18 (3.50)
Head and neck	27 (3.40)	8 (2.87)	19 (3.70)
Kidney	24 (3.03)	5 (1.79)	19 (3.70)
Leukemia	6 (0.76)	2 (0.72)	4 (0.78)
Lung*	251 (31.66)	87 (31.18)	164 (32.00)
Lymphoma	18 (2.27)	12 (4.30)	6 (1.17)
Melanoma	28 (3.53)	7 (2.51)	21 (4.09)
Mesothelioma	1 (0.13)	1 (0.36)	—
Ovary	7 (0.88)	7 (2.51)	—
Pancreas	11 (1.39)	4 (1.43)	7 (1.36)
Prostate	145 (18.28)	—	145 (28.21)
Stomach	5 (0.63)	1 (0.36)	4 (0.78)
Other sites	67 (8.45)	31 (11.11)	36 (7.00)

*These numbers represent lung cancers diagnosed as first cancers. Twelve participants, for whom lung cancer was their second cancer, were included in the analyses of lung cancer incidence and mortality (*n* = 263 lung cancer cases).

Table 5 presents the results of the analyses investigating physical activity in relation to all-site cancer and lung cancer mortality among all cancer and lung cancer cases, respectively. Age and gender were significant effect modifiers of the relations between total physical activity and cancer mortality ($P = 0.006$ and 0.001) and between moderate to vigorous activity and cancer mortality ($P = 0.04$ and 0.02). For all-site cancer mortality, total physical activity was associated with significantly reduced mortality among women (HRR, 0.68; $P = 0.005$) and among younger participants (HRR, 0.75; $P = 0.01$), but nonsignificant trends toward increased mortality among men and older participants (both $P > 0.10$). The results for moderate to vigorous activity were similar with attenuated, nonsignificant effects for women (HRR, 0.83; $P = 0.14$) and younger participants (HRR, 0.90; $P = 0.35$) and significantly higher mortality among men and older participants (both HRRs, 1.19; $P = 0.02$ and 0.03). Finally, pack-year history was an effect modifier of the relations between vigorous activity and percentage of moderate to vigorous activity that was vigorous and cancer mortality ($P = 0.04$ and 0.05). The HRRs for vigorous and percentage of vigorous activity suggested slightly increased mortality among those with lighter smoking histories (HRRs, 1.28 and 1.22; $P = 0.01$ and 0.08) and nonsignificantly, slightly reduced mortality among those with >44 pack-years of smoking (HRRs, 0.97 and 0.93; $P = 0.75$ and 0.33). There was no evidence of nonlinear trend in any analysis, and the proportional hazards assumption was met in each case.

In the analyses predicting mortality among those diagnosed with lung cancer, gender was a significant effect modifier ($P = 0.004$) such that total physical activity was related to significantly reduced mortality among women (HRR, 0.69; $P = 0.007$) but not among men (HRR, 1.15; $P = 0.15$). There was a marginally significant trend ($P = 0.05$) for vigorous activity to be associated with slightly increased mortality among participants with lighter smoking histories (HRR, 1.39; $P = 0.09$) but nonsignificantly reduced mortality among those with >44 pack-years of smoking (HRR, 0.88; $P = 0.24$). There was also a nonsignificant trend ($P = 0.09$) for moderate to vigorous activity to be associated with reduced lung cancer mortality among heavier participants (BMI >27.5 kg/m^2; HRR, 0.83; $P = 0.17$), but there was no association found for lighter participants (HRR, 1.11; $P = 0.32$). All results represent linear or dose-response effects. The proportional hazards assumption was met for each final model predicting lung cancer mortality; thus, effects are presumed constant over the follow-up time.

Table 4. Results of Cox regression models predicting cancer incidence

	Stratum	HRR	95% CI Lower	95% CI Upper	*P*
Predicting incidence of any cancer (*n* = 7,045 participants, 793 cases)					
Total physical activity (h/wk)	Male	0.86	0.80	0.94	0.07*
	Female	0.99	0.88	1.12	
Moderate-vigorous physical activity (h/wk)	Male	0.93	0.85	1.01	0.06*
	Female	1.07	0.95	1.21	
Vigorous physical activity (h/wk)	Year 1	0.68	0.54	0.86	0.001†
	Years 2-5	1.02	0.95	1.10	0.54†
% Moderate-vigorous physical activity that is vigorous‡	Year 1	0.75	0.63	0.90	0.002†
	Years 2-5	0.99	0.91	1.07	0.73†
Predicting incidence of lung cancer (*n* = 7,045 participants, 263 cases)					
Total physical activity (h/wk)	Age 54-62 y	0.84	0.69	1.03	0.04*
	Age 63-78 y	1.11	0.95	1.29	
Moderate-vigorous physical activity (h/wk)		0.99	0.87	1.11	0.83§
Vigorous physical activity (h/wk)		1.00	0.88	1.12	0.94§
% Moderate-vigorous physical activity that is vigorous‡	20-44 Pack-years	0.83	0.66	1.05	0.097*
	45-185 Pack-years	1.04	0.91	1.21	

NOTE: All HRRs presented are for a 1 SD increase in physical activity (cf. Table 1).
*For omnibus test of interaction.
†For stratum-specific test.
‡Adjusted for gender.
§For main effect test.

Table 5. Results of Cox regression models predicting cancer mortality

	Stratum	HRR	95% CI		*P*
			Lower	Upper	
Predicting any cancer mortality (*n* = 747 cases, 236 deaths)					
Total physical activity (h/wk)*	Age 54-62 y	0.75	0.59	0.94	0.006†
	Age 63-78 y	1.15	0.94	1.39	
	Male	1.15	0.96	1.38	0.001†
	Female	0.68	0.53	0.89	
Moderate-vigorous physical activity (h/wk)	Age 54-62 y	0.90	0.73	1.12	0.04†
	Age 63-78 y	1.19	1.02	1.40	
	Male	1.19	1.03	1.37	0.02†
	Female	0.83	0.64	1.07	
Vigorous physical activity (h/wk)	20-44 Pack-years	1.28	1.06	1.56	0.04†
	45-185 Pack-years	0.97	0.82	1.15	
% Moderate-vigorous physical activity that is vigorous	20-44 Pack-years	1.22	0.98	1.54	0.05†
	45-185 Pack-years	0.93	0.79	1.08	
Predicting lung cancer mortality (*n* = 231 cases, 141 deaths)					
Total physical activity (h/wk)	Male	1.15	0.95	1.40	0.004†
	Female	0.69	0.53	0.90	
Moderate-vigorous physical (h/wk)	BMI ≤27.5 kg/m^2	1.11	0.90	1.37	0.09†
	BMI >27.5 kg/m^2	0.83	0.65	1.08	
Vigorous physical activity (h/wk)	20-44 Pack-years	1.39	0.95	2.05	0.05†
	45-185 Pack-years	0.88	0.71	1.09	
% Moderate-vigorous physical activity that is vigorous‡		1.03	0.85	1.25	0.78§

NOTE: All HRRs presented are for a 1 SD increase in physical activity (cf. Table 1). Cancer cases were excluded from the mortality analyses if the date of diagnosis was in the same month or after the date of death due to reporting timing (loss of 46 all-site cancer cases and 32 lung cancer cases).
*The upper 1% and lower 5% of the distribution were excluded for undue influence (*n* = 41).
†For omnibus test of interaction.
‡Adjusted for gender, pack-years.
§For main effect test.

Discussion

This study found total physical activity to be significantly associated with lower incidence of any cancer among men but not among women, consistent with the results of the large cohort study of Thune and Lund (20). It is not clear why physical activity would be protective against all-site cancer for men but not for women. It may be an artifact of the smaller number of incident cancers among women. A post hoc power analysis revealed that we had only 64% power to detect a protective relationship in women similar to that seen among men in the cohort, where we had 94% power. It is not likely that the effects of physical activity in this study were stronger for the cancers that men developed versus those developed by the women. Aside from lung cancer, the most common type of cancer diagnosis in women in the study was breast cancer, whereas prostate cancer was most common in men; there is a much clearer evidence for the protective role of physical activity in breast cancer than for prostate cancer (5, 38).

Total physical activity was associated with modestly reduced risk of lung cancer among younger participants but not older participants, consistent with the findings of Colbert et al. (11). This suggests that the benefits of physical activity may not be great enough to counteract the carcinogenic effects of numerous years of cigarette smoking, which would likely be greater in older participants; however, controlling for pack-years and current smoking in this analysis did not change the results. In contrast with the results of the analyses predicting all-site cancer described above, this reduced incidence of lung cancer held for women as well as for men. The effect for women has not been examined extensively and is consistent with the results of three studies (12, 15, 16), which found physical activity to be protective against lung cancer in samples of women but was inconsistent with the results of Thune and Lund (20) who found no effect of physical activity on lung cancer for women. This discrepancy could simply be due to too few female cases in the Thune and Lund study; even with their much larger overall sample size, our study had almost twice the number of lung cancer cases among women.

This study found total physical activity to be associated with significantly reduced cancer mortality among younger participants and women who had been diagnosed with any cancer during the follow-up period. Furthermore, total physical activity was associated with reduced lung cancer mortality only for women. The relationship between physical activity and cancer mortality has not been studied widely, and it is not clear why physical activity would be protective for women but not for men and for younger but not for older participants. The gender discrepancy could relate to a differential effect of physical activity on mortality from cancers diagnosed in women versus those diagnosed in men or, for lung cancer, to different histologic subtypes of lung cancer, as has been reported in previous studies (15, 20). The age discrepancy cannot simply be due to decreased tobacco exposure among younger participants because stratification by pack-year history revealed protection among heavier but not lighter smokers. We were not able to control for stage at diagnosis in this analysis. If the cancers among younger participants were diagnosed at an earlier stage, then these cases might have been healthier than those with a later stage at diagnosis and would likely have higher physical activity rates.

When total physical activity was divided into subgroups based on intensity, the pattern of results was less clear. Analysis of moderate to vigorous activity produced similar results for all-site cancer incidence and for all-site cancer mortality but also showed physical activity to be associated with significantly increased risk of mortality for older participants and men. This could reflect a correlation between physically active occupations and higher smoking levels among men; however, statistical control for smoking history, current smoking status, and current employment did not change the results. We did not have data on type of employment, which would have helped to elucidate this result.

Analysis of vigorous and percentage of vigorous activity yielded two main findings. First, vigorous and percentage of vigorous physical activity were only associated with reduced risk of all-site cancer in the first year of follow-up. This result could be an artifact of some participants having lower physical activity rates in the first year due to undiagnosed cancers. However, only 2 of 16 results were found to be inconsistent across follow-up time, so evidence for such a bias was not consistent. Second, vigorous activity was associated with cancer mortality differentially by pack-years of smoking. Vigorous activity was related to modest or no reduction in mortality for those participants with heavier pack-years of smoking but increased risk of mortality among those with lighter pack-years of smoking. This result is puzzling. Other studies have found reduced risk among heavy smokers (15, 16, 20).

Analyses of total physical activity produced a much clearer pattern of results than the subanalyses of activity intensity. Additionally, vigorous activity was not consistently more protective against cancer outcomes than less vigorous physical activity. These findings suggest that total time spent in physical activities may be more important than the intensity of activity. However, our measure of physical activity might not be sensitive enough to distinguish accurately between relative intensities of physical activities. Further research is needed to clarify the roles of amount of activity and intensity in the relationship between physical activity and cancer in current and former smokers.

This study sought to determine the forms of the relationships between physical activity and cancer outcomes and the importance of physical activity intensity. Consistently, these relationships followed a linear or dose-response pattern, suggesting that more physical activity is increasingly protective against cancer incidence and mortality.

We had hoped that stratifying these analyses by age, pack-year history, or BMI would help explain the mechanisms by which physical activity may affect cancer risk and mortality among people with significant tobacco exposure. While the lack of consistent and significant effects of modification have not helped to shed light on these questions, the marginally significant effects by BMI and pack-year history underscore the need for future studies to test these variables and other potential effect modifiers to further our understanding of potential biological mechanisms.

The strengths of this study include a prospective design, large sample size of men and women with significant smoking histories, significant follow-up time, and well-documented outcomes. We also had dietary data that allowed for evaluation of dietary factors as confounders of the relationships between physical activity and cancer outcomes. Other strengths include the careful evaluation of confounding by both pack-year history and time-dependent current smoking status as well as evaluation of effect modification by pack-years of smoking, gender, age, and BMI.

One important limitation of this study is the physical activity instrument. The amounts of physical activity reported by these participants were very high, and these high amounts cannot be accounted for simply by occupational physical activity because there were high rates among the retired and unemployed groups as well. These results may be attributable in part to the physical activity assessment that classified several activities generally accepted to be sedentary as ''light activity'' and some light activities as ''moderate activity.'' It is likely that participants overestimated their rates of physical activity using the measure used in this study. We have no reason to believe that the overestimation of physical activity would be other than systematic and thus would have no effect on the relationships between physical activity and cancer outcomes. However, the sedentary activities classified as ''light activity'' and used in our measure of total physical activity may be a marker for some other factor such as social interaction, or removing oneself from a smoking environment, which could account for the effects of total physical activity on cancer outcomes.

A related limitation of this study is that physical activity was measured only once; thus, it is not known how physical activity change affects cancer outcomes. Furthermore, without knowing the frequency and duration of physical activities, it is not known how these important aspects of physical activity affect cancer outcomes. In sum, the possible biases that may result from the use of this physical activity measure at only one time point suggests a cautious interpretation of these results. The conclusions of this study would be strengthened by consistent results from future prospective studies that assess physical activity at several time points throughout the follow-up period using a more comprehensive, objectively verifiable measure of physical activity.

Additionally, this sample was predominately Caucasian and middle-aged; thus, these results may not be generalizable to other ethnic, age, or smoking groups. Results also cannot be generalized to lighter smokers (i.e., those with a <20 pack-year history) or those who had quit smoking for >6 years. Future studies should include a more demographically diverse population and recruit participants with a wider range of smoking and quitting behaviors.

Finally, this study only included a fraction of the cancer end points in the CARET study because many people were diagnosed or died of cancers prior to the measurement of physical activity, and there were more cancer end points among the group of participants who failed to provide physical activity data (data not presented). The reduction in end points significantly reduced the power to detect differences in these analyses.

Analyzing only the participants who survived to provide physical activity data may also mean that the sample on which these analyses are based is healthier than average and that physical activity would more greatly reduce the incidence and mortality from cancer in a higher-risk sample. Additionally, the reduced number of cancer and mortality cases in this study did not permit analysis of physical activity in relation to different histologic subtypes of lung cancer. Preliminary evidence is accumulating to suggest that the potential effects of physical activity may be different for different subtypes of lung cancer (15, 20); thus, future studies should attempt to investigate these relationships.

In summary, the results of this study suggest that physical activity may confer modest protection against all-site and lung cancer incidence and mortality among people with substantial smoking histories, that incidence may be more attenuated for men and mortality more attenuated for women, and that these effects may be more pronounced for younger people and may differ inconsistently by pack-years of smoking. However, given the methodologic limitations of the single crude physical activity measurement, prospective studies using more sophisticated measures of physical activity assessed at multiple time points during follow-up are needed to corroborate these associations. Further investigation of the potential role of promoting physical activity together with smoking cessation as a strategy to reduce cancer risk and mortality among smokers is needed.

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