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Original Contribution

Prospective Study of Physical Activity and Lung Cancer by Histologic Type in Current, Former, and Never Smokers

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Increased physical activity has been associated with decreased lung cancer risk. However, no previous investigation has examined physical activity in relation to lung cancer histologic types by smoking status. The authors investigated these relations in the National Institutes of Health–AARP Diet and Health Study among 501,148 men and women aged 50–71 years at baseline in 1995–1996. During follow-up to 2003, 6,745 lung carcinomas occurred (14.8% small cell, 40.3% adenocarcinoma, 19.7% squamous cell, 6.1% undifferentiated large cell, 7.2% non-small cell not otherwise specified, and 11.8% carcinoma not otherwise specified). Among former smokers, the multivariate relative risks of small cell, adenocarcinoma, squamous cell, and undifferentiated large cell carcinomas comparing the highest with the lowest activity level (≥5 times/week vs. inactive) were 0.93 (95% confidence interval (CI): 0.67, 1.28), 0.79 (95% CI: 0.67, 0.94), 0.73 (95% CI: 0.57, 0.93), and 0.61 (95% CI: 0.38, 0.98), respectively. Among current smokers, corresponding values were 0.77 (95% CI: 0.58, 1.02), 0.76 (95% CI: 0.61, 0.95), 0.85 (95% CI: 0.65, 1.11), and 1.10 (95% CI: 0.69, 1.78). In contrast, physical activity was unrelated to lung carcinoma among never smokers ($P_{interaction}$ between physical activity and smoking for total lung carcinomas = 0.002). The inverse findings among former and current smokers in combination with the null results for physical activity among never smokers may point toward residual confounding by cigarette smoking as an explanation for the relations observed.

lung neoplasms; motor activity; neoplasms by histologic type; prospective studies; smoking

Abbreviations: CI, confidence interval; RR, relative risk; SD, standard deviation.

Lung cancer is the leading cause of cancer-related deaths among men and women in the United States, accounting for 28% of cancer deaths in this country (1). Cigarette smoking is the major determinant of lung cancer, accounting for approximately 90% of cases (2). Primary prevention is the most favorable strategy for lung cancer prevention, and smoking cessation remains the most favorable way to prevent lung cancer among smokers (2).

Most (3–13), but not all (14–20), of the numerous studies that have investigated the association between physical activity and lung cancer are consistent with an inverse relation between the 2. Information on whether physical activity differentially affects histologic lung carcinoma types is much more limited, with only 5 available studies on the topic (9–13). One study (10) found an inverse relation of physical activity to small cell and adenocarcinoma but no association with squamous cell carcinoma, and another study (11) noted an inverse association with small cell and squamous cell carcinoma and no relation with large cell and adenocarcinoma. In contrast, 3 studies (9, 12, 13) reported a statistically nonsignificant inverse association with physical activity that did not appear to vary by histologic type.

The relation of smoking to lung cancer differs markedly according to histologic type, with from 4- to 10-fold greater risks from smoking seen for small cell and squamous cell carcinomas than for adenocarcinoma and undifferentiated large cell carcinoma (21). Given differential strengths of the effects of smoking on lung carcinoma histologic types,

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smoking and physical activity may plausibly interact to influence the occurrence of lung carcinoma histologic types. However, no previous study has investigated physical activity in relation to lung carcinoma histologic types according to smoking status.

In a large cohort of US men and women, we examined the effect of smoking on the relation of physical activity to major lung carcinoma histologic types. Our study differs from previous prospective investigations in being the largest available study on the topic, with 6,745 lung carcinoma cases and several hundred to several thousand cases of each major histologic type.

MATERIALS AND METHODS

Study population

The National Institutes of Health–AARP Diet and Health Study was established in 1995–1996 when an initial mailed questionnaire on medical history, diet, and physical activity was mailed to 3.5 million AARP (formerly known as the American Association of Retired Persons) members aged 50–71 years and residing in 1 of 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) (22). A total of 566,402 persons satisfactorily returned the questionnaire and, of these, we excluded individuals with a previous diagnosis of cancer other than nonmelanoma skin cancer (n = 52,561), as well as those with missing information on physical activity (n = 5,911) or missing or inconsistent information on smoking habits (n = 6,782). The analytical cohort comprised the remaining 501,148 subjects. The study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Cohort follow-up

Study participants were followed up through December 31, 2003, by annual linkage of the cohort to the National Change of Address database maintained by the US Postal Service and its processing of undeliverable mail, various address change update services, and directly from cohort members' notifications. In addition, vital status was ascertained by annual linkage of the cohort to the Social Security Administration's Death Master File in the United States. Follow-up searches of presumed deaths in the National Death Index Plus provided verification and information on cause of death.

Endpoint ascertainment

Incident cases of lung carcinoma were identified by probabilistic linkage to the state cancer registries serving our cohort. We recently expanded our cancer registry ascertainment area by 3 states (Texas, Arizona, and Nevada) to capture cancer cases occurring among participants who moved to those states during follow-up. The North American Association of Central Cancer Registries certifies all 11 cancer registries (23). We conducted a validation study comparing registry findings with self-reports and medical records and found that approximately 90% of all cancer cases in our cohort were validly identified by using linkage to cancer registries (24).

The endpoint in the present analysis was first primary incident lung carcinoma. We also investigated the main histologic types of lung carcinoma, defined by anatomic site and histologic code of the *International Classification of Diseases for Oncology*, Third Edition (ICD-O codes 34.0–34.9) (25). We considered the following (histologic code): small cell (8002, 8041, 8042, 8044, 8045), adenocarcinoma (8140, 8200, 8231, 8250, 8251, 8260, 8290, 8310, 8323, 8430, 8480, 8481, 8490, 8550), squamous cell (8050, 8070, 8071, 8072, 8073, 8074), undifferentiated large cell (8012, 8020, 8021, 8022, 8031, 8032), non-small cell not otherwise specified (8046, 8560), and lung carcinomas not otherwise specified (8010, 8011, 8123, 8562). Non-small cell carcinomas included adenocarcinoma, squamous cell, undifferentiated large cell, and non-small cell not otherwise specified carcinomas.

Cases of fatal lung cancer that had not been diagnosed with incident lung cancer (and for which we hence lacked cancer registry data) contributed person-time to the study up to their date of death, at which point they were censored and not included as cases. In addition to our main analyses, we conducted a separate analysis of physical activity in relation to lung cancer mortality. In that subanalysis, cases of fatal lung cancer contributed person-time to the study up to their date of death.

Assessment of physical activity and smoking

The baseline questionnaire inquired about physical activity during the previous year, defined as the frequency each week spent at activities that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat. There were 6 possible response options: never, rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, and 5 or more times per week. Our physical activity assessment corresponds to the American College of Sports Medicine's physical activity guidelines that recommend at least 20 minutes of continuous vigorous exercise 3 times per week for improving cardiorespiratory fitness (26).

Although our measure of physical activity has not been directly compared with referent instruments, a questionnaire very similar to the one used in our study showed good reliability (percentage agreement = 0.76; kappa = 0.53) and reasonable validity (percentage agreement = 0.71; kappa = 0.40) as assessed by an activity monitor (27).

In a subset of study participants (n = 310,105), we collected information on light and moderate to vigorous intensity physical activity. We used those data to assess whether the observed relations with vigorous activity also held for less vigorous forms of activity.

Participants reported if they had smoked more than 100 cigarettes during their lifetime, the number of cigarettes they smoked per day, whether they were currently smoking or had quit smoking, and the number of years since quitting, if applicable. We used that information to create categories

Table 1. Baseline Characteristics in 1995–1996 According to Physical Activity, NIH–AARP Diet and Health Study

Characteristic[a]	Physical Activity, times per week[b]				
	0	<1	1–2	3–4	≥5
Participants, no.	92,150	68,673	108,454	134,427	97,444
Age, years	62.2	61.2	61.6	62.3	62.4
Gender, %					
Women	48.9	41.3	38.4	37.0	33.3
Men	51.1	58.7	61.6	63.0	66.7
Smoking status, %					
Current smoker	21.8	17.7	14.7	10.6	9.6
≤20 cigarettes/day	13.1	11.1	9.6	7.2	6.4
>20 cigarettes/day	8.7	6.6	5.1	3.4	3.2
Former smoker	45.4	48.2	49.2	52.7	53.9
Quit ≥10 years ago	32.3	36.4	37.9	41.6	43.1
Quit 1–9 years ago	13.0	11.7	11.4	11.1	10.8
Never smoker	32.8	34.1	36.1	36.7	36.4
Body mass index, kg/m^2	28.5	27.8	27.2	26.5	26.0
College education, %	27.6	36.9	40.6	44.2	44.1
Married or living as married, %	62.0	68.3	70.7	72.4	73.7
Family history of cancer, %	50.6	51.9	51.4	51.2	50.9
Fruit and vegetable intakes, servings/1,000 kcal per day	3.1	3.2	3.4	3.7	3.9
Red meat intake, g/1,000 kcal per day	38.0	37.3	36.2	32.5	30.7
Alcohol intake, servings/week	7.0	7.0	6.8	6.7	7.3
Nonsteroidal antiinflammatory drug use, %	49.1	52.4	51.8	52.2	49.2

Abbreviation: NIH, National Institutes of Health.

[a] All values (except age) were directly standardized to the age distribution of the cohort. All percentages for categorical variables represent column percentages.

[b] Physical activity is defined as activities that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat.

of smoking status (never, former, current), smoking intensity (1–10, 11–20, 21–30, 31–40, 41–60, ≥61 cigarettes per day), and time since quitting (≥10 years, 5–9 years, 1–4 years, <1 year).

Statistical analysis

Cox proportional hazards regression (28) with person-time of follow-up as the time scale was used to estimate relative risks and the corresponding 95% confidence intervals of lung carcinoma. Using age as the time scale yielded similar results. We tested for and found no departures from the proportional hazards assumption. Follow-up time was calculated from the scan date of the baseline questionnaire until the first occurrence of 1 of the following events: diagnosis of lung carcinoma, move out of the registry ascertainment area, death, or the end of follow-up on December 31, 2003.

Participants were divided into 5 categories according to their physical activity level: 0 (inactive), less than 1, 1–2, 3–4, and 5 or more times per week. The group of inactive participants served as the reference group. Tests of linear trend across increasing categories of physical activity were conducted by assigning the mean level of physical activity for categories and treating that term as a single continuous variable. We assessed lung carcinoma risk in 3 models: one adjusting for age and gender; one adjusting for age, gender, smoking status, smoking dose, and time since quitting; and one additionally adjusting for body mass index, race/ethnicity, marital status, family history of any cancer, education, and intakes of fruit and vegetables, red meat, and alcohol. In extensive initial analyses, we had ruled out confounding by numerous variables, including by dietary supplement use. Missing values for covariates were included in the models as a separate category. Risk estimates were calculated for total lung carcinoma and histologic types of lung carcinoma separately.

To examine whether the association between physical activity and risk of lung carcinoma was modified by other potential risk factors for lung carcinoma, we conducted both stratified analyses and formal tests of interaction; the statistical significance of the latter was evaluated by using likelihood-ratio tests. All relative risks are presented with 95% confidence intervals, and reported P values are based on 2-sided tests.

All analyses were conducted by using SAS, release 8.2, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The mean ages at baseline and at the end of follow-up were 61.9 (standard deviation (SD), 5.4) and 69.1 (SD, 5.5) years, respectively. At baseline, 18% of the cohort reported not being physically active, and 19% indicated engaging in physical activity 5 or more times per week. Physical activity was positively associated with elements of a healthy lifestyle, including less smoking, lower body mass index, greater dietary intakes of fruit and vegetables, and less consumption of red meat. In addition, active participants were more likely to report a college education and to be married than their less active counterparts (Table 1).

Lung carcinoma risk was inversely associated with body mass index and educational level, and it was suggestively inversely related to intakes of fruit and vegetables. In contrast, lung carcinoma risk was positively associated with smoking, family history of cancer, and intakes of red meat and alcohol (data not tabulated).

During 3,600,331 person-years of follow-up (mean follow-up, 7.2 years; SD, 1.4), we documented 6,745 lung carcinoma cases, of which 14.8% were small cell, 40.3% were adenocarcinoma, 19.7% were squamous cell, 6.1% were undifferentiated large cell, 7.2% were non-small cell not otherwise specified, and 11.8% were lung carcinoma not otherwise specified. The risk of total lung carcinoma decreased in a linear fashion with increasing physical activity level (Table 2). In analyses that were adjusted for age and gender, participants who reported engaging in physical activity 5 or more times per week had a relative risk of 0.50 (95% confidence interval (CI): 0.46, 0.54; $P_{trend} < 0.001$) as compared with their inactive counterparts. After additional control for smoking status (current, former, or never smoking), the inverse association was substantially attenuated (relative risk (RR) = 0.68, 95% CI: 0.63, 0.74; not shown in Table 2). When we further adjusted for the combination of smoking intensity and time since quitting, the relation became slightly weaker, but it remained statistically significant (RR = 0.77, 95% CI: 0.71, 0.83). Additional control for other potential confounding variables had little impact. When we examined physical activity in relation to mortality from lung cancer (n = 4,793 cases), the multivariate relative risk was 0.79 (95% CI: 0.72, 0.87).

Undiagnosed lung carcinoma may have caused subjects to report a lower physical activity level at the time the baseline questionnaire was administered, which would bias our results. After we excluded all cases of lung carcinoma that occurred during the first 4 years of follow-up (n = 3,260 lung carcinoma cases excluded), results were not materially altered (multivariate RR comparing extreme categories = 0.82, 95% CI: 0.74, 0.92). Findings were also virtually unchanged when we further minimized any impact that undiagnosed lung carcinoma may have had on physical activity levels by additionally excluding subjects who reported poor health at entry (n = 3,392 lung carcinoma cases excluded; RR = 0.83, 95% CI: 0.74, 0.93). When we repeated our analysis of excluding the first 4 years of follow-up, this time using mortality from lung cancer as an endpoint, the corresponding relative risk was 0.80 (95% CI: 0.71, 0.93).

Using data from a subcohort of study participants for whom we had a separate assessment of physical activity that included information on light and moderate to vigorous physical activity (n = 3,836 cases), we found that both light activity (multivariate RR for >7 hours of activity per week vs. no activity = 0.85, 95% CI: 0.76, 0.95) and moderate to vigorous activity (multivariate RR for >7 hours of activity per week vs. no activity = 0.82, 95% CI: 0.74, 0.90) were inversely related to lung carcinoma.

We next investigated physical activity in relation to histologic types of lung carcinoma (Table 2).As in our analysis of total lung carcinoma, adjustment for smoking accounted for most of the difference between the age- and gender-adjusted models and the multivariate models. Physical activity showed an inverse or suggestively inverse relation with all histologic subtypes. The relative risks for small cell, adenocarcinoma, squamous cell, and undifferentiated large cell carcinomas were 0.82 (95% CI: 0.67, 1.01), 0.80 (95% CI: 0.71, 0.91), 0.78 (95% CI: 0.65, 0.93), and 0.86 (95% CI: 0.62, 1.21), respectively.

When we repeated the histology-specific analyses among cases of fatal lung cancer for which we had both incidence and mortality data, the corresponding relative risks for small cell, adenocarcinoma, squamous cell, and undifferentiated large cell carcinomas were 0.83 (95% CI: 0.66, 1.05), 0.86 (95% CI: 0.73, 1.02), 0.74 (95% CI: 0.59, 0.94), and 0.88 (95% CI: 0.59, 1.32), respectively.

Because lung carcinomas among ever smokers and never smokers may be differentially influenced by physical activity, we conducted additional analyses that were stratified by smoking status (Table 3). Increased physical activity was similarly related to decreased risk of total lung carcinoma among both current and former smokers ($P_{interaction}$ = 0.301). In contrast, no relation of physical activity to total lung carcinoma was noted among never smokers, and that null association differed significantly from the inverse relation with physical activity observed among ever smokers ($P_{interaction}$ = 0.002).

On evaluation of lung carcinoma subtypes by smoking status, we observed a similar pattern of an inverse association with physical activity among current and former smokers and no relation among never smokers for most histologic types, although the difference in the relation of physical activity to lung carcinoma by smoking status (ever vs. never smokers) was statistically significant only for total non-small cell lung carcinoma ($P_{interaction}$ = 0.006) and, within that group, for adenocarcinoma ($P_{interaction}$ = 0.019) (Table 3). For the group of current smokers, the

Table 2. Relative Risk of Total Lung Carcinoma and Histologic Type of Lung Carcinoma According to Physical Activity, NIH–AARP Diet and Health Study, 1995–2003

Histologic Type of Lung Carcinoma	Physical Activity, times per week[a,b]													P_{trend}
	0		<1			1–2			3–4			≥5		
	No. of Cases	Relative Risk	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval	
Total lung carcinomas (n = 6,745)	1,759		995			1,425			1,534			1,032			
Age and gender adjusted		1.0		0.77	0.71, 0.83		0.67	0.62, 0.72		0.55	0.51, 0.59		0.50	0.46, 0.54	<0.001
Age and gender adjusted + smoking[c]		1.0		0.89	0.82, 0.96		0.86	0.81, 0.93		0.81	0.76, 0.87		0.77	0.71, 0.83	<0.001
Full multivariate[d]		1.0		0.91	0.84, 0.99		0.89	0.83, 0.96		0.84	0.78, 0.90		0.78	0.72, 0.85	<0.001
Small cell (n = 1,001)	298		142			201			218			142			
Age and gender adjusted		1.0		0.65	0.54, 0.80		0.56	0.47, 0.68		0.47	0.39, 0.56		0.42	0.34, 0.51	<0.001
Age and gender adjusted + smoking[c]		1.0		0.78	0.64, 0.95		0.79	0.66, 0.94		0.80	0.67, 0.96		0.76	0.62, 0.93	0.031
Full multivariate[d]		1.0		0.80	0.66, 0.98		0.82	0.68, 0.98		0.86	0.72, 1.03		0.82	0.67, 1.01	0.190
Total non-small cell (n = 4,945)	1,223		753			1,051			1,141			777			
Age and gender adjusted		1.0		0.84	0.76, 0.92		0.71	0.65, 0.77		0.58	0.54, 0.63		0.54	0.49, 0.59	<0.001
Age and gender adjusted + smoking[c]		1.0		0.95	0.87, 1.04		0.90	0.83, 0.97		0.83	0.77, 0.91		0.80	0.73, 0.87	<0.001
Full multivariate[d]		1.0		0.98	0.89, 1.07		0.92	0.84, 1.00		0.85	0.78, 0.93		0.80	0.73, 0.88	<0.001
Adenocarcinoma (n = 2,718)	643		406			591			635			443			
Age and gender adjusted		1.0		0.87	0.76, 0.98		0.77	0.69, 0.86		0.64	0.57, 0.71		0.60	0.53, 0.68	<0.001
Age and gender adjusted + smoking[c]		1.0		0.97	0.85, 1.10		0.95	0.85, 1.06		0.86	0.77, 0.96		0.84	0.74, 0.95	<0.001
Full multivariate[d]		1.0		0.97	0.86, 1.10		0.94	0.84, 1.05		0.84	0.75, 0.94		0.80	0.71, 0.91	<0.001
Squamous cell (n = 1,328)	362		205			258			305			198			
Age and gender adjusted		1.0		0.75	0.63, 0.89		0.56	0.48, 0.66		0.50	0.43, 0.58		0.43	0.36, 0.51	<0.001
Age and gender adjusted + smoking[c]		1.0		0.89	0.75, 1.06		0.76	0.65, 0.90		0.79	0.68, 0.92		0.72	0.61, 0.86	<0.001
Full multivariate[d]		1.0		0.95	0.80, 1.13		0.82	0.70, 0.97		0.87	0.74, 1.02		0.78	0.65, 0.93	0.010
Undifferentiated large cell (n = 412)	101		67			102			81			61			
Age and gender adjusted		1.0		0.91	0.67, 1.24		0.84	0.64, 1.11		0.51	0.38, 0.68		0.51	0.37, 0.71	<0.001
Age and gender adjusted + smoking[c]		1.0		1.05	0.77, 1.43		1.08	0.82, 1.43		0.75	0.56, 1.01		0.80	0.58, 1.10	0.017
Full multivariate[d]		1.0		1.08	0.79, 1.47		1.12	0.85, 1.48		0.78	0.58, 1.14		0.86	0.62, 1.21	0.031
Non-small cell not otherwise specified (n = 487)	117		75			100			120			75			
Age and gender adjusted		1.0		0.86	0.64, 1.15		0.68	0.53, 0.90		0.62	0.48, 0.80		0.52	0.39, 0.70	<0.001
Age and gender adjusted + smoking[c]		1.0		0.97	0.73, 1.30		0.87	0.67, 1.14		0.91	0.70, 1.18		0.80	0.60, 1.08	0.169
Full multivariate[d]		1.0		1.00	0.75, 1.34		0.90	0.69, 1.18		0.92	0.71, 1.20		0.80	0.59, 1.09	0.160
Carcinoma not otherwise specified (n = 799)	238		100			173			175			113			
Age and gender adjusted		1.0		0.58	0.46, 0.74		0.61	0.50, 0.74		0.47	0.38, 0.57		0.41	0.32, 0.51	<0.001

Age and gender adjusted + smoking[c]	1.0	0.68	0.54, 0.86	0.80	0.66, 0.97	0.70	0.58, 0.86	0.64	0.51, 0.81	<0.001
Full multivariate[d]	1.0	0.71	0.56, 0.90	0.84	0.69, 1.03	0.75	0.61, 0.91	0.68	0.54, 0.85	0.004

Abbreviation: NIH, National Institutes of Health.

[a] Physical activity is defined as activities that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat.

[b] Physical activity: 0 times per week (644,668 person-years); <1 time per week (493,585 person-years); 1–2 times per week (782,822 person-years); 3–4 times per week (973,623 person-years); ≥5 times per week (705,633 person-years).

[c] Adjustment for smoking included the combination of smoking status (never, former, current), time since quitting for former smokers (≥10 years, 5–9 years, 1–4 years, <1 year), and smoking intensity for former and current smokers (1–10, 11–20, 21–30, 31–40, 41–60, ≥61 cigarettes/day).

[d] The multivariate models used age as the underlying time metric and included the following covariates: gender (women, men); body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0 kg/m^2); a combination of smoking status (never, former, current), time since quitting for former smokers (≥10 years, 5–9 years, 1–4 years, <1 year), and smoking intensity for former and current smokers (1–10, 11–20, 21–30, 31–40, 41–60, ≥61 cigarettes/day); race/ethnicity (white, black, Hispanic, and other race/ethnicity); education (less than high school, high school, vocational school or some college, college graduate, and postgraduate); marital status (married or living as married, other); family history of cancer (yes, no); intakes of fruit and vegetables combined (quintiles); red meat (quintiles); and alcohol (0, <1, 1–3, >3 servings/day).

inverse association with physical activity was most apparent for adenocarcinoma.

To evaluate whether the association between physical activity and lung carcinoma was modified by gender, age, race, education, body mass index, history of emphysema, intakes of fruit and vegetables, red meat, and alcohol, and use of nonsteroidal antiinflammatory drugs, we repeated our analyses within subgroups defined by those variables (Table 4). Physical activity was related to decreased lung carcinoma risk in almost all subgroups, suggesting no important effect modification (all $P_{\text{interaction}} > 0.05$).

DISCUSSION

In this prospective study of 501,148 men and women, increased physical activity appeared to be associated with a decrease in the risk of total lung carcinoma of 22%. The association persisted after controlling for established or suspected risk factors for lung carcinoma, including smoking. The inverse relation was apparent for all histologic subtypes of lung carcinomas.

Our findings for total lung carcinoma confirm the majority of previous reports that physical activity is inversely related to risk of lung cancer. Eight prospective (3, 4, 7–10, 12, 13) and 3 case-control (5, 6, 11) studies observed a 23%–42% decreased risk of lung cancer for high versus low levels of total physical activity (7, 8, 10, 12) or certain types of physical activity (4, 13), although inverse relations were limited to subgroup analyses in some studies (3, 4, 9). Risk reduction tended to be more pronounced in studies with less comprehensive adjustment for smoking (5, 7). In contrast, 4 prospective investigations (14, 16–18), 1 retrospective cohort study (19), and 1 case-control study (15) found no association between physical activity and lung cancer. One case-control study (20) observed a positive association of physical activity and lung cancer risk. Inconsistent findings from previous reports may be due to limited sample sizes (3, 4, 7, 8, 14, 17, 18), imprecise assessments of physical activity (15, 20), insufficient variability in physical activity (10), variation in the magnitude of residual confounding by smoking (3–18, 20), or potential recall bias (5, 6, 11, 15, 19, 20).

Reasonably comprehensive information on smoking enabled us to examine the association between physical activity and risk of lung carcinoma according to specific subgroups defined by the combination of smoking status, smoking intensity, and time since quitting smoking. Consistent with most (6, 11, 12), but not all (7), previous studies that presented data stratified by smoking status, our study found no association between physical activity and total lung carcinoma among never smokers. It has been suggested that the etiology of lung cancer among never smokers is distinct from that among smokers (29, 30).

We noted a progressive attenuation of the relation between physical activity and lung carcinoma with increasing control for smoking. In addition, physical activity was inversely associated with lung carcinoma among current and former smokers. Because smoking is associated with both physical activity levels and lung cancer risk and is

Table 3. Multivariate Relative Risk of Total Lung Carcinoma and Histologic Type of Lung Carcinoma According to Physical Activity in Participants Defined by Smoking Status, Smoking Intensity, and Time Since Quitting Smoking, NIH–AARP Diet and Health Study, 1995–2003[a]

Histologic Type of Lung Carcinoma	No. of Cases	Physical Activity, times per week									P_{trend}
		0	<1		1–2		3–4		≥5		
		Relative Risk	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	
Total lung carcinomas											
Current smoker	3,063	1.0	0.88	0.78, 0.97	0.88	0.80, 0.97	0.84	0.76, 0.94	0.77	0.68, 0.87	<0.001
≤20 cigarettes/day	1,683	1.0	0.93	0.81, 1.08	0.91	0.80, 1.04	0.85	0.74, 0.98	0.78	0.66, 0.93	0.002
>20 cigarettes/day	1,380	1.0	0.81	0.69, 0.95	0.85	0.73, 0.98	0.84	0.72, 0.98	0.75	0.62, 0.91	0.010
Former smoker	3,364	1.0	0.94	0.83, 1.05	0.87	0.79, 0.97	0.82	0.74, 0.91	0.78	0.70, 0.87	<0.001
Quit 1–9 years ago	1,523	1.0	0.86	0.72, 1.02	0.85	0.73, 0.99	0.78	0.67, 0.90	0.74	0.63, 0.87	<0.001
Quit ≥10 years ago	1,841	1.0	1.02	0.86, 1.20	0.91	0.78, 1.05	0.87	0.75, 1.00	0.83	0.71, 0.96	0.004
Never smoker	318	1.0	1.02	0.81, 1.86	1.28	0.89, 1.84	1.08	0.75, 1.56	1.02	0.69, 1.52	0.504
Small cell											
Current smoker	614	1.0	0.83	0.65, 1.06	0.80	0.64, 1.01	0.84	0.66, 1.06	0.77	0.58, 1.02	0.100
≤20 cigarettes/day	322	1.0	0.91	0.65, 1.28	0.87	0.63, 1.18	0.79	0.57, 1.10	0.87	0.60, 1.26	0.296
>20 cigarettes/day	292	1.0	0.75	0.53, 1.06	0.74	0.53, 1.03	0.91	0.66, 1.26	0.65	0.42, 1.01	0.199
Former smoker	366	1.0	0.75	0.51, 1.09	0.84	0.61, 1.16	0.87	0.65, 1.18	0.93	0.67, 1.28	0.915
Quit 1–9 years ago	206	1.0	0.76	0.47, 1.22	0.84	0.56, 1.27	0.77	0.52, 1.16	0.93	0.61, 1.43	0.833
Quit ≥10 years ago	160	1.0	0.74	0.40, 1.35	0.85	0.51, 1.41	1.01	0.63, 1.62	0.94	0.56, 1.55	0.676
Never smoker	21	1.0	0.71	0.13, 3.92	1.06	0.28, 4.05	1.32	0.38, 4.61	0.47	0.08, 2.68	0.692
Total non-small cell											
Current smoker	2,076	1.0	0.96	0.84, 1.09	0.93	0.83, 1.06	0.88	0.77, 1.00	0.83	0.71, 0.96	0.006
≤20 cigarettes/day	1,148	1.0	1.03	0.86, 1.23	0.97	0.82, 1.15	0.93	0.79, 1.11	0.84	0.69, 1.03	0.059
>20 cigarettes/day	928	1.0	0.88	0.72, 1.06	0.89	0.75, 1.07	0.82	0.68, 1.00	0.82	0.65, 1.03	0.049
Former smoker	2,604	1.0	0.96	0.84, 1.09	0.87	0.77, 0.98	0.81	0.72, 0.91	0.75	0.66, 0.85	<0.001
Quit 1–9 years ago	1,123	1.0	0.91	0.75, 1.10	0.83	0.70, 0.99	0.76	0.64, 0.90	0.68	0.56, 0.83	<0.001
Quit ≥10 years ago	1,481	1.0	1.00	0.83, 1.21	0.91	0.77, 1.07	0.86	0.74, 1.01	0.82	0.69, 0.97	0.006
Never smoker	265	1.0	1.47	0.93, 2.30	1.33	0.87, 1.99	1.12	0.75, 1.69	1.11	0.72, 1.72	0.981
Adenocarcinoma											
Current smoker	1,018	1.0	0.96	0.80, 1.16	0.90	0.76, 1.07	0.82	0.68, 0.98	0.76	0.61, 0.95	0.004
≤20 cigarettes/day	582	1.0	1.01	0.79, 1.29	0.90	0.71, 1.13	0.84	0.66, 1.07	0.75	0.56, 1.01	0.024
>20 cigarettes/day	436	1.0	0.92	0.70, 1.21	0.92	0.71, 1.19	0.80	0.60, 1.06	0.78	0.56, 1.10	0.080
Former smoker	1,497	1.0	0.95	0.79, 1.12	0.92	0.78, 1.08	0.83	0.71, 0.97	0.79	0.67, 0.94	0.002
Quit 1–9 years ago	581	1.0	0.99	0.75, 1.29	0.82	0.64, 1.05	0.76	0.60, 0.97	0.82	0.63, 1.06	0.051
Quit ≥10 years ago	916	1.0	0.92	0.72, 1.18	0.99	0.80, 1.22	0.87	0.71, 1.07	0.79	0.63, 0.98	0.016
Never smoker	203	1.0	1.30	0.76, 2.23	1.50	0.93, 2.40	1.23	0.77, 1.97	1.20	0.73, 1.99	0.990
Squamous cell											
Current smoker	645	1.0	0.96	0.76, 1.21	0.84	0.67, 1.05	0.92	0.73, 1.15	0.85	0.65, 1.11	0.278
≤20 cigarettes/day	335	1.0	1.20	0.86, 1.66	0.97	0.71, 1.34	1.09	0.80, 1.50	0.96	0.66, 1.40	0.785
>20 cigarettes/day	310	1.0	0.76	0.54, 1.07	0.72	0.52, 1.00	0.77	0.55, 1.07	0.77	0.53, 1.13	0.195

Table continues

Table 3. Continued

Histologic Type of Lung Carcinoma	No. of Cases	Physical Activity, times per week									P_{trend}
		0	<1		1–2		3–4		≥5		
		Relative Risk	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	
Former smoker	663	1.0	0.90	0.70, 1.18	0.80	0.63, 1.01	0.82	0.66, 1.03	0.73	0.57, 0.93	0.022
Quit 1–9 years ago	341	1.0	0.74	0.51, 1.07	0.83	0.61, 1.14	0.79	0.58, 1.07	0.58	0.41, 0.84	0.012
Quit ≥10 years ago	322	1.0	1.13	0.77, 1.66	0.76	0.52, 1.11	0.89	0.63, 1.24	0.91	0.64, 1.29	0.521
Never smoker	20	1.0	2.01	0.47, 8.42	0.86	0.19, 3.91	0.75	0.17, 3.25	0.55	0.10, 2.82	0.164
Undifferentiated large cell											
Current smoker	195	1.0	0.85	0.54, 1.36	1.32	0.90, 1.94	0.85	0.55, 1.33	1.10	0.69, 1.78	0.958
≤20 cigarettes/day	109	1.0	0.72	0.38, 1.42	1.49	0.90, 2.45	0.73	0.39, 1.36	1.16	0.62, 2.16	0.991
>20 cigarettes/day	86	1.0	0.99	0.52, 1.88	1.08	0.59, 1.96	1.01	0.54, 1.91	0.99	0.47, 2.08	0.992
Former smoker	197	1.0	1.23	0.79, 1.92	0.89	0.58, 1.37	0.65	0.42, 1.00	0.61	0.38, 0.98	0.002
Quit 1–9 years ago	89	1.0	1.24	0.63, 2.46	1.18	0.64, 2.19	0.95	0.51, 1.76	0.49	0.51, 1.76	0.045
Quit ≥10 years ago	108	1.0	1.19	0.66, 2.15	0.68	0.37, 1.24	0.46	0.25, 0.84	0.64	0.36, 1.17	0.020
Never smoker	20	1.0	2.28	0.50, 10.42	1.42	0.31, 6.51	1.75	0.42, 7.36	1.22	0.23, 6.40	0.976
Non-small cell not otherwise specified											
Current smoker	218	1.0	0.99	0.65, 1.50	1.07	0.74, 1.57	1.08	0.65, 1.57	0.84	0.52, 1.37	0.699
≤20 cigarettes/day	122	1.0	0.97	0.56, 1.70	0.92	0.55, 1.54	1.15	0.69, 1.90	0.72	0.37, 1.41	0.676
>20 cigarettes/day	96	1.0	1.02	0.55, 1.91	1.30	0.75, 2.27	0.97	0.52, 1.81	1.04	0.51, 2.11	0.939
Former smoker	247	1.0	0.94	0.61, 1.45	0.77	0.51, 1.15	0.83	0.57, 1.21	0.71	0.47, 1.07	0.133
Quit 1–9 years ago	112	1.0	0.84	0.46, 1.52	0.67	0.39, 1.17	0.60	0.35, 1.02	0.48	0.26, 0.90	0.015
Quit ≥10 years ago	135	1.0	1.09	0.57, 2.07	0.93	0.51, 1.69	1.16	0.68, 1.99	1.02	0.57, 1.83	0.807
Never smoker	22	1.0	1.59	0.42, 6.00	0.51	0.11, 2.29	0.46	0.11, 1.90	0.92	0.25, 3.43	0.562
Carcinoma not otherwise specified											
Current smoker	373	1.0	0.56	0.40, 0.78	0.75	0.57, 0.99	0.70	0.52, 0.94	0.51	0.35, 0.75	0.004
≤20 cigarettes/day	213	1.0	0.56	0.36, 0.87	0.72	0.50, 1.04	0.61	0.41, 0.90	0.45	0.27, 0.76	0.005
>20 cigarettes/day	160	1.0	0.56	0.33, 0.94	0.79	0.51, 1.21	0.85	0.55, 1.32	0.61	0.34, 1.09	0.290
Former smoker	394	1.0	0.98	0.70, 1.39	0.95	0.70, 1.29	0.85	0.63, 1.14	0.85	0.62, 1.17	0.202
Quit 1–9 years ago	194	1.0	0.64	0.38, 1.10	0.98	0.64, 1.48	0.90	0.60, 1.35	0.90	0.58, 1.41	0.989
Quit ≥10 years ago	200	1.0	1.37	0.86, 2.20	0.94	0.60, 1.50	0.82	0.53, 1.28	0.83	0.52, 1.33	0.086
Never smoker	32	1.0	0.21	0.03, 1.76	1.25	0.46, 3.35	0.77	0.27, 2.21	0.83	0.27, 2.60	0.927

Abbreviation: NIH, National Institutes of Health.

[a] The multivariate models were adjusted for the following covariates: gender (women, men); body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0 kg/m^2); race/ethnicity (white, black, Hispanic, and other race/ethnicity); education (less than high school, high school, vocational school or some college, college graduate, and postgraduate); marital status (married or living as married, other); family history of cancer (yes, no); intakes of fruit and vegetables combined (quintiles); red meat (quintiles); and alcohol (0, <1, 1–3, >3 servings/day), as well as for smoking by using the combination of smoking status (never, former, current), time since quitting for former smokers (≥10 years, 5–9 years, 1–4 years, <1 year), and smoking intensity for former and current smokers (1–10, 11–20, 21–30, 31–40, 41–60, ≥61 cigarettes/day). In each case, the stratification variable was excluded from the model. Within each stratum, the category of inactive subjects served as the reference group.

Table 4. Multivariate Relative Risk of Total Lung Carcinoma According to Physical Activity in Participants Defined by Selected Variables, NIH–AARP Diet and Health Study, 1995–2003[a]

Variable	No. of Cases	Physical Activity, times per week									P_{trend}	$P_{interaction}$
		0	<1		1–2		3–4		≥5			
		Relative Risk	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval		
Gender												
Men	4,419	1.0	0.92	0.84, 1.02	0.85	0.78, 0.93	0.80	0.74, 0.88	0.77	0.70, 0.85	<0.001	0.059
Women	2,326	1.0	0.88	0.77, 1.00	0.95	0.84, 1.07	0.90	0.80, 1.01	0.80	0.69, 0.92	0.006	
Age at baseline												
<65 years	3,391	1.0	0.93	0.84, 1.04	0.93	0.84, 1.02	0.83	0.75, 0.92	0.80	0.72, 0.90	<0.001	0.200
≥65 years	3,354	1.0	0.89	0.79, 1.00	0.85	0.77, 0.95	0.84	0.76, 0.93	0.76	0.68, 0.85	<0.001	
Race												
White	6,285	1.0	0.92	0.85, 1.00	0.89	0.82, 0.96	0.84	0.78, 0.90	0.78	0.72, 0.85	<0.001	0.864
Nonwhite	460	1.0	0.82	0.60, 1.11	0.95	0.73, 1.24	0.87	0.67, 1.13	0.86	0.64, 1.15	0.374	
Education												
Some college or less	4,980	1.0	0.94	0.86, 1.02	0.90	0.83, 0.98	0.85	0.79, 0.93	0.76	0.70, 0.84	<0.001	0.377
College graduate or postgraduate	1,765	1.0	0.84	0.71, 0.99	0.85	0.73, 0.98	0.79	0.68, 0.91	0.81	0.69, 0.95	0.023	
Body mass index, kg/m^2												
<25.0	2,773	1.0	0.89	0.78, 1.00	0.87	0.78, 0.97	0.80	0.72, 0.90	0.75	0.67, 0.85	<0.001	0.673
25.0–29.9	2,755	1.0	0.96	0.85, 1.09	0.92	0.82, 1.03	0.84	0.75, 0.94	0.83	0.74, 0.94	<0.001	
≥30.0	1,217	1.0	0.87	0.73, 1.03	0.87	0.74, 1.02	0.92	0.78, 1.09	0.73	0.60, 0.90	0.027	
History of emphysema												
No	6,000	1.0	0.95	0.88, 1.03	0.92	0.85, 0.99	0.88	0.82, 0.95	0.83	0.76, 0.90	<0.0001	0.664
Yes	745	1.0	0.82	0.65, 1.03	0.93	0.76, 1.11	0.75	0.61, 0.91	0.70	0.54, 0.91	0.003	
Fruit and vegetable intakes[b]												
Low	4,131	1.0	0.91	0.83, 1.00	0.84	0.77, 0.92	0.80	0.73, 0.88	0.79	0.71, 0.88	<0.001	0.142
High	2,614	1.0	0.92	0.80, 1.06	0.99	0.87, 1.11	0.90	0.80, 1.01	0.80	0.70, 0.91	<0.001	
Red meat intake[c]												
Low	2,818	1.0	0.87	0.76, 0.99	0.86	0.76, 0.96	0.84	0.75, 0.93	0.76	0.67, 0.85	<0.001	0.703
High	3,927	1.0	0.94	0.85, 1.04	0.91	0.84, 1.00	0.84	0.76, 0.92	0.81	0.73, 0.90	<0.001	
Alcohol use[d]												
No	1,653	1.0	0.85	0.72, 1.00	0.89	0.78, 1.03	0.87	0.76, 1.00	0.78	0.66, 0.91	0.006	0.643
Yes	5,092	1.0	0.93	0.85, 1.02	0.89	0.82, 0.97	0.83	0.76, 0.90	0.79	0.72, 0.86	<0.001	

NSAID use[e]												
No	1,803	1.0	0.93	0.80, 1.09	0.90	0.79, 1.04	0.84	0.74, 0.97	0.87	0.75, 1.02	0.044	0.753
Yes	1,586	1.0	0.86	0.73, 1.01	0.85	0.73, 0.99	0.83	0.72, 0.97	0.77	0.65, 0.91	0.007	

Abbreviations: NIH, National Institutes of Health; NSAID, nonsteroidal antiinflammatory drug.

[a] The multivariate models were adjusted for the following covariates: gender (women, men); body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0 kg/m^2); a combination of smoking status (never, former, current), time since quitting for former smokers (≥10 years, 5–9 years, 1–4 years, <1 year), and smoking intensity for former and current smokers (1–10, 11–20, 21–30, 31–40, 41–60, ≥61 cigarettes/day); race/ethnicity (white, black, Hispanic, and other race/ethnicity); education (less than high school, high school, vocational school or some college, college graduate, and postgraduate); marital status (married or living as married, other); family history of cancer (yes, no); intakes of fruit and vegetables combined (quintiles); red meat (quintiles); and alcohol (0, <1, 1–3, >3 servings/day). In each case, the stratification variable was excluded from the model. Within each stratum, the category of inactive subjects served as the reference group.

[b] The strata of low and high fruit and vegetable intakes are defined on the basis of the cutpoint representing the median value of 3.2 servings/1,000 kcal per day.

[c] The strata of low and high red meat intakes are defined on the basis of the cutpoint representing the median value of 31.4 g/1,000 kcal per day.

[d] The strata of low and high nonalcoholic beverage intakes are defined on the basis of the cutpoint representing the median value of 1,782 mL/day.

[e] The analysis that was stratified by NSAID use was conducted by using data from a subcohort of study participants for whom we had collected information regarding NSAID use.

imperfectly measured, residual confounding by cigarette smoking is a reasonable explanation for the apparently protective effect of physical activity seen in smokers, because one would expect to observe an inverse association between physical activity and lung cancer among both smokers and never smokers if the physical activity and lung cancer relation were causal.

In theory, physical activity may decrease lung carcinoma risk by increasing pulmonary ventilation and perfusion (31–34), thereby reducing the amount of time potential carcinogens, including tobacco-specific nitrosamines, reside in the airways (35, 36). Physical activity may also reduce the risk of lung carcinoma by attenuating a smoking-related decline in lung function (32), which represents a strong predictor of lung cancer (37, 38). This mechanism may be operative even after smoking cessation, although we do not believe that this hypothesis alone can explain the similarity in the relations between physical activity and lung carcinoma that we observed among current and former smokers. In addition, physical activity may protect against lung carcinoma risk by counteracting oxidative DNA damage (39–41) or enhancing DNA repair capacity, both of which play a critical role in lung carcinogenesis (42, 43). The beneficial effect of physical activity on lung carcinoma risk also may be due to its influence on immune destruction of errant cells, because regular physical activity enhances immune function (44, 45).

We observed a similar risk reduction of total lung carcinoma afforded by physical activity in both women and men, among younger and older subjects, for highly educated and less highly educated individuals, for lean and overweight participants, and for those with low and high intakes of fruits and vegetables, red meat, and alcohol. In contrast, some studies have noted that the association between physical activity and lung cancer varies according to gender (3, 4), body mass index (11), or age (3, 9).

An important strength of our study is the substantial size of the cohort, yielding more than 4 times the number of cases than any previous prospective study on the topic. This resulted in relatively more precise risk estimates for physical activity. Subjects with preexisting cancer at baseline were excluded from the analyses in order to reduce the influence that malignant disease may have had on physical activity levels at entry. In secondary analyses, we further minimized the potential for bias due to preexisting but undiagnosed lung carcinoma by excluding the first 4 years of follow-up.

Measurement error in the assessment of physical activity was a potential concern, in particular because our questionnaire has not been directly compared with validation instruments (46). However, a physical activity instrument very similar to ours has demonstrated reasonable validity and reproducibility (27). Moreover, our prospective study design precluded bias attributable to differential recall of physical activity by participants with and without lung carcinoma. The large size of our cohort with the associated costs prohibited us from using more accurate measures of physical activity, such as activity monitors (47). Similarly, we relied on self-reported data from questionnaires for other potential confounding variables such as dietary intake and supplement use, which were also subject to measurement errors.

In conclusion, our data show that increased physical activity is associated with reduced risk of total lung carcinoma and individual lung carcinoma histologic types among current and former smokers. These relations, however, may be due to residual confounding by cigarette smoking. Our study's finding of no association between physical activity and lung carcinoma among never smokers is consistent with a noncausal relation with physical activity. The most important individual and public health strategy for lung cancer prevention is to discourage smoking initiation among adolescents and to advocate for smoking cessation among tobacco users of any age.

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論文名	Prospective study of physical activity and lung cancer by histologic type in current, former, and never smokers
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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	50～71(62歳)	[redacted]		( )		前向きコホート
	対象数	10000以上			( )		( )
調査の方法		質問紙	( )				
アウトカム	予 防	なし	なし	ガン予防	なし		( )
	維持・改善	な し	な し	な し	なし	( )	( )
図 表		なし					
図表掲載箇所							

概 要 (800字まで)

＜目的＞肺がん発症と身体活動との関係を明らかにすること。＜方法＞コホート名：The National Institutes of Health-AARP Diet and Health Study、対象者数：566402人、追跡期間：7.2年、因子評価方法詳細：直近の1年間に“汗をかいたり、心拍数が上がるような20分以上の身体活動を生活活動、勤労活動、余暇で週何回行いましたか”の質問に基づき、なし 1回未満 1～2回 3～4回 5回以上の5つの分位に分類した。因子の単位：回／週。＜結果＞高強度身体活動と全肺がん発症リスクとの関係は、分位1：1、分位2：0.91(0.84-0.99)、分位3：0.89(0.83-0.96)、分位4：0.84(0.78-0.9)、分位5：0.78(0.72-0.85)であった。

結 論 (200字まで)

週あたり0-1回の汗をかいたり 心拍数の上がるような20分以上の高強度運動は全肺がんリスクを低下させる。

エキスパートによるコメント (200字まで)

余暇活動、生活活動の区別なくわずか週20分の高強度身体活動を行うことで、肺がん発症を予防できることを示した点で、意義のある研究である。

担当者 宮地元彦

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ORIGINAL PAPER

Physical activity and head and neck cancer risk

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Abstract
Objective To investigate the relation of physical activity to head and neck cancer.
Methods We prospectively examined the association between physical activity and head and neck cancer in 487,732 men and women, who, at baseline in 1995–1996, were 50–71 years old and free of cancer and emphysema. Follow-up occurred through 31 December 2003.
Results During follow-up, 1,249 participants developed head and neck cancer, of which 42.0%, 18.9%, and 32.5% were located in the oral cavity, pharynx, and larynx, respectively. In analyses adjusted for age and gender, the relative risks (RR) of head and neck cancer for increasing frequency of physical activity (0, < 1, 1–2, 3–4, and ≥5 times per week) were 1.0 (reference), 0.76, 0.66, 0.57, and 0.62 (95% CI = 0.52–0.74), respectively (p for trend < 0.001). After multivariate adjustment including smoking, the relation was attenuated and became statistically non-significant (RR comparing extreme physical activity categories = 0.89, 95% CI = 0.74–1.06; p for trend = 0.272). In analyses of head and neck cancer subtypes, the corresponding RRs for cancers of the oral cavity, pharynx, and larynx were 0.98 (95% CI = 0.75–1.29), 0.70 (95% CI = 0.45–1.08), and 0.82 (95% CI = 0.59–1.13), respectively.
Conclusions Our findings suggest that physical activity is unlikely to play an important role in the prevention of head and neck cancer.

Keywords Head and neck cancer · Oral cavity cancer · Pharynx cancer · Larynx cancer · Physical activity

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Introduction

Head and neck cancer is a significant global health problem, accounting for over 600,000 new cancers diagnosed each year [1]. Head and neck cancer includes tumors of the oral cavity, pharynx, and larynx [2]. The incidence rate of head and neck cancer is three- to fourfold higher among men than women [1]. Tobacco use and alcohol drinking have been consistently associated with increased risk of head and neck cancer and these two variables account for 75% of head and neck cancer cases [3]. Few other modifiable lifestyle factors have been identified that may affect this highly fatal cancer [2, 4].

Increasing evidence suggests that physical activity plays an important role in the prevention of cancer [5]. Physical activity may influence head and neck carcinogenesis

specifically because physical activity modulates specific mucosal immune parameters, such as salivary immunogloblin (Ig) A [6–9] and saliva composition has been linked to head and neck cancer risk due to persistent saliva exposure of the epithelial mucosa of the oral cavity, pharynx, and larynx [10].

Despite the global significance of head and neck cancer and the possibility of a preventive physical activity mechanism, little attention has been directed toward exploring the association between physical activity and head and neck cancer. Available information comes from three previous studies of squamous head and neck cancers [11–13]. Those three investigations [11–13] observed no association between physical activity and individual cancer sites within the head and neck. No study has evaluated the association between physical activity and total head and neck cancer.

We prospectively examined physical activity in relation to subsequent incidence of head and neck cancer in a large study of initially healthy middle-aged and elderly men and women from the United States (U.S.). Due to possible distinct etiologies of cancers of the oral cavity, pharynx, and larynx, we explored whether associations with physical activity varied by cancer site within the head and neck.

Material and methods

Study population

The NIH-AARP Diet and Health Study is a prospective cohort that was established in 1995–1996 when 566,402 members of AARP (formerly known as American Association of Retired Persons) aged 50–71 years and residing in one of six U.S. states (CA, FL, LA, NJ, NC, and PA) or two metropolitan areas (Atlanta, GA, and Detroit, MI) returned a mailed questionnaire on medical history, diet, and physical activity [14]. Of responding individuals, we excluded persons who reported a previous diagnosis of cancer other than non-melanoma skin cancer ($n = 52{,}561$) or emphysema ($n = 13{,}764$), those with missing information on physical activity ($n = 5{,}705$), and those with missing or inconsistent information on smoking habits ($n = 6{,}640$). The analytic cohort of the present report includes 487,732 subjects (295,253 men and 192,479 women). The study was approved by the Special Studies Institutional Review Board (IRB) of the U.S. National Cancer Institute.

Cohort follow-up and endpoint ascertainment

Cohort follow-up was performed by regular linkage to the National Change of Address database maintained by the U.S. Postal Service and through processing of undeliverable mail, other address change update services, and directly from cohort members' notifications. Vital status was ascertained by linkage of the cohort to the Social Security Administration Death Master File in the U.S. Follow-up searches of presumed deaths in the National Death Index Plus provided verification and information on cause of death. For matching purposes, we have virtually complete data on first and last name, address history, gender, and date of birth. Study participants were followed-up through 31 December 2003.

Incident cases of head and neck cancer were identified by probabilistic linkage to the state cancer registries serving our cohort. We recently expanded our cancer registry ascertainment area by three states (TX, AZ, and NV) to capture cancer cases occurring among participants who moved to those states during follow-up. The North American Association of Central Cancer Registries certifies all eleven cancer registries [15]. We conducted a validation study comparing registry findings to self-reports and medical records and found that approximately 90% of all cancer cases in our cohort were validly identified using linkage to cancer registries [16].

The endpoints in the current analysis were classified by anatomic site and histologic code according to the International Classification of Disease for Oncology (ICD-O), third edition [17]. All newly incident cases of squamous head and neck cancer (histology code 8050–8076) were considered for analysis. Oral cavity cancers included tumors of the lips (C00.1–C00.9), tongue (C01.9–C02.9), gums (C03.0–C03.9), floor of the mouth (C04.0–C04.9), palate (C05.0–C05.9), and other parts of the mouth (C06.0–C06.9). Cancers of the pharynx included tumors of the tonsil (C09.0–C09.9), oropharynx (C10.0–C10.9), piriform sinus (C12.9), hypopharynx (C13.0–C13.9), and pharynx not otherwise specified (NOS) (C14.0). Laryngeal cancer included tumors with site codes C32.0–C32.9 and squamous histology. The overarching category of head and neck cancer included cancers of the oral cavity, pharynx, larynx, and squamous cell carcinomas at other anatomical sites of the head and neck or overlapping regions of the lip, oral cavity, and pharynx.

Physical activity assessment

At baseline, a mailed questionnaire inquired about physical activity during the previous year, defined as the frequency each week spent at activities that lasted 20 min or more and caused either increases in breathing or heart rate or working up a sweat. Six possible response options were given: never; rarely; 1–3 times per month; 1–2 times per week; 3–4 times per week; and 5 or more times per week. Our physical activity assessment corresponds to the

American College of Sports Medicine (ACSM) physical activity guidelines that recommend at least 20 min of continuous vigorous exercise three times per week for improving cardio-respiratory fitness [18]. A questionnaire very similar to the one used in our cohort showed good reliability (percentage agreement = 0.76; kappa = 0.53) and reasonable validity (percentage agreement = 0.71; kappa = 0.40) as assessed by a computer science and applications (CSA) physical activity monitor [19].

In a subset of study participants we collected data on light and moderate to vigorous intensity physical activity. We used that information to evaluate associations with less vigorous forms of activity.

Statistical analysis

All statistical analyses were conducted using SAS release 9.1 (SAS Institute, Cary, NC). Cox proportional hazards regression [20] with person-time as the time scale was used to estimate hazard ratios of head and neck cancer, computed as relative risks (RR) with corresponding 95% CI. Using age as the time scale yielded similar results. We tested for and found no departures from the proportional hazards assumption. Follow-up time was calculated from the scan date of the baseline questionnaire until the first occurrence of one of the following events: diagnosis of head and neck cancer, diagnosis of esophageal or stomach cancer (as a diagnosis of one of those cancers would be associated with increased surveillance of the other sites), date moved out of the cancer registry catchment area, death, or the end of follow-up (31 Dec 2003).

Participants were divided into five categories according to their physical activity level: 0 (less than once per month), <1, 1–2, 3–4, and 5 or more times per week. The group with the lowest physical activity level served as the reference group. Tests of linear trend across increasing categories of physical activity were conducted by assigning the mean level of physical activity for categories and treating that term as a single continuous variable. We assessed head and neck cancer risk in three models, one model adjusting for age and gender, a second model adjusting for age, gender, and a combination of smoking status (never; former; current), time since quitting for former smokers (10+ years; 5–9 years; 1–4 years; <1 year), and smoking intensity for former and current smokers (1–10; 11–20; 21–30; 31–40; 41–60; 61+ cigarettes/day), and a third model additionally adjusting for body mass index (<18.5; 18.5–24.9; 25.0–29.9; 30.0–34.9; 35.0–39.9; ≥40.0 kg/m^2), race/ethnicity (White; Black; Hispanic; and other race/ethnicity), education (less than high school; high school; vocational school or some college; college graduate; and postgraduate), marital status (married or living as married; other), family history of cancer (yes; no), intakes of fruit and vegetables combined (quintiles), red meat (quintiles), and alcohol (0; <1; 1–3; >3 servings/day). Risk estimates were calculated for total head and neck cancer and oral, pharyngeal, and laryngeal cancers separately.

In order to examine potential effect modification of the association between physical activity and head and neck cancer, we conducted stratified analyses. We also performed tests for interaction using cross-product terms, the statistical significance of which was evaluated using likelihood-ratio tests. In a subset of study participants, we collected information on non-steroidal anti-inflammatory drug (NSAID) use. We used those data to assess whether relations with physical activity were modified by NSAID use. All p values are based on two-sided tests.

Results

During follow-up, the 487,732 participants accrued 3,518,483 total person-years. The mean (SD) ages at entry and exit were 61.9 (5.4) and 69.1 (5.5) years, respectively. The mean durations (ranges) of follow-up in censored participants without head and neck cancer and those who developed head and neck cancer were 7.2 years (range: 1 day to 8.2 years) and 3.8 years (range: 5 days to 7.8 years), respectively.

At baseline, over half of the participants reported cigarette smoking either at present or in the past, and three-fourths of the study subjects indicated consuming alcohol on a regular basis. Specifically, participants who were current, former, and never smokers at baseline contributed 13.4%, 49.9%, and 36.7%, respectively, of the total person-time. Likewise, those who drank alcohol contributed 76% of person-time, whereas those who abstained from alcohol contributed 24% of person-time.

At study entry, 19.6% of the cohort reported engaging in a minimum of 20 min of physical activity five or more times per week, and 17.9% stated that they engaged in 20 min of continuous activity less than once per month. On average, participants who reported being physically active tended to be leaner, to be college graduates, to be married, and to have higher intakes of fruit, vegetables, and alcohol than their less active counterparts. Active individuals were also less likely to currently smoke than less active participants (Table 1). Physical activity level decreased in a stepwise fashion with increasing category of BMI (data not shown).

We documented 1,249 total head and neck cancer cases, of which 42.0% were located in the oral cavity, 18.9% in the pharynx, 32.5% in the larynx, and 6.6% at other locations of the head and neck. In analyses adjusted for age and gender only, we found a strong inverse association between physical activity and head and neck cancer. Participants

Table 1 Baseline characteristics according to physical activity

Characteristics[a]	Physical activity (times per week)[b]				
	0	<1	1–2	3–4	≥5
Participants (n)	87,222	66,853	106,058	131,852	95,747
Gender (%)					
Men	50.6	58.5	61.4	68.9	66.6
Women	49.4	41.5	38.6	37.1	33.4
Smoking status (%)					
Current smoker	20.7	17.1	14.2	10.2	9.4
≤20 cigarettes/day	12.8	10.9	9.4	7.1	6.3
>20 cigarettes/day	8.0	6.2	4.8	3.2	3.0
Former smoker	44.8	48.0	49.0	52.5	53.7
Quit ≥ 10 years ago	32.8	36.7	38.1	41.7	43.2
Quit 1–9 years ago	12.0	11.3	10.9	10.8	10.4
Never smoker	34.5	34.9	36.8	37.3	36.9
Age (years)	62.0	61.1	61.5	62.2	62.4
Body-mass index (kg/m^2)	28.6	27.8	27.2	26.6	26.0
Race					
White	89.2	91.5	92.3	91.6	92.4
Non-White	10.8	8.5	7.7	8.4	7.6
College education (%)	28.1	37.3	40.9	44.5	44.4
Married or living as married (%)	62.1	68.4	70.8	72.5	73.8
Family history of cancer (%)	50.6	51.8	51.4	51.2	50.9
Fruit and vegetable intakes (servings/1,000 kcal/day)	3.1	3.2	3.4	3.7	3.9
Red meat intake (grams/1,000 kcal/day)	37.8	37.2	36.1	32.4	30.6
Alcohol intake (servings/week)	6.8	6.9	6.7	6.6	7.3
NSAID user (%)	49.4	52.4	51.9	52.3	49.3

[a] All values (except age) were directly standardized to the age distribution of the cohort

[b] Physical activity is defined as activities that lasted 20 min or more and caused either increases in breathing or heart rate or working up a sweat

who reported engaging in physical activity five or more times per week had a RR of 0.62 (95% CI = 0.52–0.74) compared to those who participated in physical activity less than once per month (Table 2). However, when we further adjusted for smoking the relation was substantially attenuated and became statistically non-significant (RR = 0.86; 95% CI = 0.72–1.03). Additional control for other potential confounding variables including BMI, race/ethnicity, marital status, family history of any cancer, education, intakes of fruit and vegetables, red meat, and alcohol had only minor influence on the risk estimate (RR = 0.89; 95% CI = 0.74–1.06).

Using information from a subset of participants for whom we had a separate assessment of physical activity that included data on light and moderate to vigorous physical activity, we observed that both light activity (multivariate RR for >7-h activity per week versus no activity = 1.07; 95% CI = 0.83–1.39) and moderate to vigorous activity (multivariate RR for >7-h activity per week versus no activity = 0.81; 95% CI = 0.64–1.03) were not statistically significantly associated with head and neck cancer.

We next evaluated the relation of physical activity to cancers of the oral cavity, pharynx, and larynx separately (Table 2). Similar to the associations observed with total head and neck cancer, for each cancer site, we found inverse relations with physical activity in analyses that were adjusted for age and gender only. The age- and gender-adjusted RRs of cancers of the oral cavity, pharynx, and larynx comparing the highest to the lowest physical activity category were 0.73 (95% CI = 0.56–0.95), 0.48 (95% CI = 0.32–0.73), and 0.52 (95% CI = 0.38–0.71), respectively. After adjustment for smoking, risk estimates became considerably weaker and were rendered statistically non-significant. The impact of control for additional potential confounders was small. The corresponding RRs of cancers of the oral cavity, pharynx, and larynx were 0.98 (95% CI = 0.75–1.29), 0.70 (95% CI = 0.45–1.08), and 0.82 (95% CI = 0.59–1.13), respectively.

We also examined whether the effect of physical activity was modified by potential risk factors for head and neck cancer (Table 3). Null associations between increasing levels of physical activity and risk of total head and neck cancer were noted across subgroups defined by gender, smoking status, age, race/ethnicity, education, BMI, intakes of fruit and vegetables, red meat, alcohol, and NSAID use. Statistically significant tests for interaction were seen for the association between physical activity and

Table 2 Relative risk of total head and neck cancer and head and neck cancer subtypes according to physical activity

Head and neck cancer type	Physical activity (times per week)[a]					*p* for trend
	0	<1	1–2	3–4	≥5	
Person-years	616,503	482,118	767,821	957,476	694,565	
Total head and neck cancer (n = 1,249)						
No. of cases	290	178	256	289	236	
Age, gender-adjusted RR (95% CI)[b]	1.0	0.76 (0.63–0.91)	0.66 (0.56–0.78)	0.57 (0.48–0.67)	0.62 (0.52–0.74)	<0.001
Age, gender-adjusted RR + smoking (95% CI)[b,c]	1.0	0.84 (0.69–1.01)	0.79 (0.67–0.94)	0.77 (0.66–0.91)	0.86 (0.72–1.03)	0.142
Full multivariate RR (95% CI)[d]	1.0	0.87 (0.72–1.05)	0.84 (0.70–0.99)	0.82 (0.69–0.97)	0.89 (0.74–1.06)	0.272
Oral cavity (n = 525)						
No. of cases	119	70	111	115	110	
Age, gender-adjusted RR (95% CI)[b]	1.0	0.74 (0.55–1.08)	0.71 (0.55–0.92)	0.57 (0.44–0.74)	0.73 (0.56–0.95)	0.015
Age, gender-adjusted RR + smoking (95% CI)[b,c]	1.0	0.81 (0.59–1.08)	0.83 (0.64–1.08)	0.73 (0.56–0.95)	0.95 (0.73–1.24)	0.749
Full multivariate RR (95% CI)[d]	1.0	0.863 (0.61–1.11)	0.86 (0.66–1.12)	0.77 (0.59–1.00)	0.98 (0.75–1.29)	0.956
Pharynx (n = 236)						
No. of cases	57	35	49	59	36	
Age, gender-adjusted RR (95% CI)[b]	1.0	0.74 (0.49–1.13)	0.63 (0.43–0.93)	0.59 (0.41–0.85)	0.48 (0.32–0.73)	0.001
Age, gender-adjusted RR + smoking (95% CI)[b,c]	1.0	0.83 (0.55–1.27)	0.77 (0.53–1.14)	0.82 (0.56–1.18)	0.68 (0.44–1.04)	0.136
Full multivariate RR (95% CI)[d]	1.0	0.88 (0.58–1.35)	0.84 (0.57–1.23)	0.88 (0.61–1.29)	0.70 (0.45–1.08)	0.180
Larynx (n = 406)						
No. of cases	97	64	81	95	69	
Age, gender-adjusted RR (95% CI)[b]	1.0	0.81 (0.59–1.11)	0.61 (0.45–0.82)	0.54 (0.41–0.72)	0.52 (0.38–0.71)	<0.001
Age, gender-adjusted RR + smoking (95% CI)[b,c]	1.0	0.92 (0.67–1.26)	0.77 (0.57–1.04)	0.79 (0.59–1.06)	0.79 (0.57–1.08)	0.137
Full multivariate RR (95% CI)[d]	1.0	0.96 (0.69–1.32)	0.82 (0.60–1.10)	0.84 (0.63–1.12)	0.82 (0.59–1.13)	0.225

[a] Physical activity is defined as activities that lasted 20 min or more and caused either increases in breathing or heart rate or working up a sweat

[b] RR = relative risk. CI = confidence interval

[c] Adjustment for smoking included the combination of smoking status (never; former; current), time since quitting for former smokers (10+ years; 5–9 years; 1–4 years; <1 year), and smoking intensity for former and current smokers (1–10; 11–20; 21–30; 31–40; 41–60; 61+ cigarettes/day)

[d] The multivariate models used age as the underlying time metric and included the following covariates: gender (women; men), body mass index (<18.5; 18.5–24.9; 25.0–29.9; 30.0–34.9; 35.0–39.9; ≥40.0 kg/m^2), a combination of smoking status (never; former; current), time since quitting for former smokers (10 + years; 5–9 years; 1–4 years; < 1 year), and smoking intensity for former and current smokers (1–10; 11–20; 21–30; 31–40; 41–60; 61 + cigarettes/day), race/ethnicity (White; Black; Hispanic; and other race/ethnicity), education (less than high school; high school; vocational school or some college; college graduate; and postgraduate), marital status (married or living as married; other), family history of cancer (yes; no), intakes of fruit and vegetables combined (quintiles), red meat (quintiles), and alcohol (0; <1; 1–3; >3 servings/day)

Table 3 Multivariate relative risk of total head and neck cancer according to physical activity in participants defined by selected variables

Variable	No. of cases	Physical activity (times per week)					*p* for	
		0	<1	1–2	3–4	≥5	trend	interaction
Gender								
Men	977	1.0	0.86 (0.69–1.07)	0.72 (0.59–0.88)	0.78 (0.65–0.95)	0.82 (0.67–1.00)	0.162	0.029
Women	272	1.0	0.86 (0.58–1.29)	1.33 (0.96–1.86)	0.90 (0.62–1.31)	1.14 (0.77–1.71)	0.768	
Smoking status								
Current smoker	487	1.0	0.85 (0.65–1.12)	0.87 (0.68–1.12)	0.79 (0.60–1.04)	0.93 (0.69–1.25)	0.493	0.985
Former smoker	551	1.0	0.91 (0.67–1.22)	0.78 (0.59–1.03)	0.83 (0.64–1.08)	0.89 (0.68–1.16)	0.567	
Never smoker	211	1.0	0.84 (0.50–1.40)	0.89 (0.58–1.39)	0.85 (0.56–1.38)	0.88 (0.56–1.38)	0.688	
Age at baseline (years)								
<65	718	1.0	0.93 (0.73–1.18)	0.87 (0.69–1.08)	0.75 (0.59–0.95)	0.90 (0.71–1.15)	0.202	0.392
≥65	531	1.0	0.77 (0.57–1.06)	0.79 (0.60–1.03)	0.89 (0.69–1.15)	0.87 (0.66–1.14)	0.829	
BMI (kg/m^2)								
<25.0	505	1.0	0.89 (0.66–1.21)	0.89 (0.68–1.18)	0.82 (0.62–1.07)	0.92 (0.69–1.21)	0.526	0.957
25.0–29.9	512	1.0	0.85 (0.63–1.16)	0.84 (0.64–1.09)	0.87 (0.67–1.14)	0.86 (0.65–1.15)	0.571	
≥30.0	232	1.0	0.85 (0.57–1.25)	0.72 (0.49–1.05)	0.70 (0.47–1.04)	0.95 (0.63–1.45)	0.593	
Race/ethnicity								
White	1,179	1.0	0.87 (0.72–1.06)	0.84 (0.70–0.99)	0.82 (0.69–0.98)	0.89 (0.75–1.08)	0.357	0.966
Nonwhite	70	1.0	0.83 (0.39–1.77)	0.81 (0.40–1.62)	0.70 (0.35–1.40)	0.73 (0.35–1.54)	0.359	
Education								
Some college or less	822	1.0	1.03 (0.83–1.29)	0.90 (0.73–1.11)	0.94 (0.76–1.15)	0.92 (0.74–1.15)	0.385	0.037
College graduate or postgraduate	427	1.0	0.57 (0.40–0.82)	0.69 (0.51–0.92)	0.61 (0.45–0.82)	0.78 (0.57–1.05)	0.518	
Fruit and vegetable intakes								
Low	808	1.0	0.82 (0.66–1.03)	0.79 (0.65–0.97)	0.81 (0.66–0.99)	0.80 (0.64–1.01)	0.115	0.352
High	441	1.0	1.06 (0.74–1.52)	0.99 (0.72–1.38)	0.91 (0.66–1.24)	1.11 (0.81–1.52)	0.703	
Red meat intake								
Low	510	1.0	1.03 (0.76–1.39)	1.06 (0.80–1.39)	0.76 (0.57–1.00)	0.96 (0.73–1.27)	0.238	0.032
High	739	1.0	0.79 (0.62–1.00)	0.72 (0.58–0.90)	0.87 (0.71–1.08)	0.85 (0.67–1.08)	0.729	
Alcohol use								
No	315	1.0	1.08 (0.75–1.57)	1.21 (0.87–1.67)	0.95 (0.68–1.32)	0.84 (0.58–1.21)	0.156	0.031
Yes	934	1.0	0.81 (0.65–1.00)	0.73 (0.60–0.89)	0.77 (0.63–0.94)	0.89 (0.73–1.10)	0.649	
NSAID use								
No	329	1.0	0.72 (0.49–1.06)	0.91 (0.66–1.26)	0.77 (0.56–1.07)	0.79 (0.56–1.13)	0.291	0.182
Yes	307	1.0	0.91 (0.63–1.32)	0.64 (0.45–0.93)	0.72 (0.51–1.01)	0.89 (0.63–1.29)	0.637	

The multivariate models were adjusted for covariates listed in Table 2 footnote. In each case, the stratification variable was excluded from the model. Within each stratum, the category representing the lowest level of physical activity served as the reference group. NSAID = non-steroidal anti-inflammatory drug. The analysis that was stratified by NSAID use was conducted using data from a sub-cohort of study participants for whom we had collected information regarding NSAID use

head and neck cancer according to gender, education, red meat intake, and alcohol use. However, inspection of the point estimates and the tests for trend across increasing categories of physical activity among participants within strata of those variables revealed no divergent patterns. Similar results were observed for cancer sites within the head and neck (data not shown).

Discussion

The findings of the current report—the first to our knowledge to present data on the relation of physical activity to total head and neck cancer—suggest that physical activity is unlikely to play an important role in the development of head and neck cancer. In addition, we detected no significant relationship between physical activity and individual cancer sites of the head and neck. The lack of a statistically significant association between physical activity and total head and neck cancer and its subtypes was consistent across strata of major covariates. In particular, tobacco smoking and alcohol use did not appear to modify results.

Although our risk estimates linking physical activity to head and neck cancer were in the inverse direction, our overall interpretation of a largely null association is consistent with other available studies [11–13] on the topic. One retrospective cohort study ($n = 92$ cases) from Denmark [11] compared physically active mail carriers with the general population and reported standardized incidence ratios (SIRs) of 0.91, 1.08, 1.16, 0.97, and 1.31 for individual cancers of the larynx, pharynx, mouth, lip, and tongue, none of which were statistically significant. Similarly, one case-control study of laryngeal cancer ($n = 779$ cases) from Turkey [12] (OR = 1.20; 95% CI = 0.90–1.60) and one case-control study of laryngeal cancer ($n = 285$ cases) and buccal cavity cancer ($n = 499$ cases) from the U.S. [13] observed no statistically significant association with physical activity (OR = 0.5; 95% CI = 0.3–1.0 and OR = 1.1; 95% CI = 0.8–1.7, respectively).

Despite the lack of an association with head and neck cancer observed in our study, we noted some difference in the relation of physical activity to head and neck cancer toward a stronger inverse association in men than women. Physical activity levels were greater among men than women in our study, which suggests that potentially disparate physical activity levels between genders do not explain the greater incidence rate of head and neck cancer among men compared to women [21].

Apart from the true absence of an association between physical activity and head and neck cancer, we considered several possible alternative explanations for our findings. Data on physical activity was assessed using self-report, which generally involves some extent of misclassification [22]. Any random imprecision in measuring physical activity would tend to bias the relationship between physical activity and head and neck cancer toward the null hypothesis. Also, it is possible that we did not capture physical activity at the time during which it plays an important etiologic role in head and neck carcinogenesis.

Insufficient variation in physical activity as a possible reason for the null association is improbable because our physical activity measure showed marked-variation in the expected direction across levels of BMI. Also, greater physical activity on this scale was associated with reduced risk of total mortality and death due to heart disease in our cohort [23]. In addition, a physical activity instrument comparable to the one used in our study has documented validity and reproducibility [19]. Thus, measurement error in our assessment of physical activity is not likely to fully explain the null association in our data. It is possible that our questionnaire format may have been associated with some degree of over-reporting of activity. Circumstantial data indicate that self-administered activity questions can lead to inflated estimates of the reported time spent engaging in physical activity as compared with interviewer-administered assessments [22]. Notwithstanding this potential limitation, the main possible correlates of activity over-reporting, including age and body size were accounted for in our multivariate statistical analyses.

Our study lacked information on participant income and occupation, factors that could confound the relation of physical activity to head and neck cancer. Nonetheless, we would expect uncontrolled confounding by income to result in a spurious exaggeration of a potentially inverse association between physical activity and head and neck cancer. By comparison, confounding by occupation could conceivably have obscured a possible physical activity benefit, because some occupations are associated with high activity levels but low socioeconomic status, a potential risk factor for head and neck cancer [24]. Notwithstanding these caveats, we did control for at least some potential confounding by income and occupation by adjusting for education level, a variable correlated with income and occupation as well as with head and neck cancer [24]. Strict control for tobacco and alcohol as well as for other potential risk factors for head and neck cancer further minimized the potential for confounding.

We did not collect data on infections by human papillomavirus (HPV) and Epstein-Barr virus (EBV), putative risk factors for cancer at some sites in the head and neck [25, 26], but those agents are not considered to be closely associated with physical activity [27] and are therefore unlikely to have affected our results.

Other methodologic biases are probably also not responsible for the lack of an association seen in our data. Specifically, participants with preexisting cancer and