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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 immunoglobulin (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

emphysema at baseline were removed from the analyses to lessen the impact that malignant or chronic disease may have had on physical activity levels at baseline. Exposure information was gathered prior to cancer diagnosis, which precluded bias ascribable to discrepant recall of physical activity level by participants with and without a diagnosis of head and neck cancer.

Due to the large size of our cohort including more than 1,200 cases of head and neck cancer, insufficient statistical power is not likely to account for the null associations observed in our study. The large number of cases facilitated a detailed exploration of the relations with physical activity across strata of major risk factors for head and neck cancer. We observed null findings within all strata, which gave us confidence that we did not miss a strong inverse association between physical activity and head and neck cancer in our analyses.

In theory, physical activity has the potential to influence head and neck carcinogenesis through its effects on immune function. The impact of physical activity on immunomodulation varies according to the level of exercise. As compared to sitting, low-intensity physical activity, such as walking increases circulating levels of immune parameters, including blood counts for neutrophils, lymphocytes, monocytes, and natural killer cells [28]. Moderate levels of exercise also enhance mucosal immune parameters, such as salivary IgA [6, 7, 9]. In contrast, vigorous levels of exercise decrease T and B cells [29] and transiently suppress natural killer cell cytotoxicity [30] and salivary IgA [8]. We observed statistically non-significant relations for head and neck cancer both with vigorous activity and with less vigorous forms of activity. Even so, the possibility of a physical activity effect on the content or composition of saliva is intriguing, because saliva continuously permeates the mucosal epithelium of the oral cavity, the pharynx and, to a lesser extent the larynx, and therefore bears potential to influence head and neck cancer risk [10].

We conclude that despite the existence of a plausible biological mechanism, physical activity is not likely to substantially impact upon total head and neck cancer risk. Since definitive conclusions cannot be drawn on the basis of findings from the limited body of currently existing data on this topic, the relation of physical activity to head and neck cancer deserves continued attention in future epidemiologic research.

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