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Dietary fiber and grain consumption in relation to head and neck cancer in the NIH-AARP Diet and Health Study

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Abstract

Background—Dietary fiber and grain consumption may reduce the risk of head and neck cancer; however, the epidemiological evidence is limited. We investigated this relationship in the National Institutes of Health (NIH)-AARP Diet and Health Study.

Methods—Cox proportional hazards models were used to calculate multivariable hazard ratios (HR) and 95% confidence intervals (CI) to investigate dietary fiber and grain intake in relation to head and neck cancer.

Results—During approximately 11 years of follow-up, 1,867 (401 women/1,466 men) cases of head and neck cancer were diagnosed. Our data indicated that the relationship between fiber and grain intake and head and neck cancer is modified by sex (*p*-interactions <0.001 and 0.001, respectively). Women with higher intake of total fiber and total grains had a lower risk of head and neck cancer ($HR_{10g/day}$=0.77, 95% CI=0.64-0.93; $HR_{serving/1000kcal}$ =0.89, 95% CI=0.80-0.99, respectively); this inverse relation was consistent across subtypes of fiber and grains. Conversely in men, the inverse associations were weaker and nonsignificant.

Conclusions—In the largest prospective cohort study to investigate this relation to date, intake of total fiber and grain foods was inversely associated with head and neck cancer incidence among women, but not men.

Keywords

diet; fiber; grains; head and neck cancer; prospective study

Introduction

Head and neck cancer encompasses those in the oral cavity, oropharynx, hypopharynx, and larynx [1]; collectively, they represent the sixth most common cancer worldwide, with an annual incidence of approximately 400,000 cases, of which two-thirds occur in developing countries [2]. In the United States, head and neck cancer accounts for approximately 3.2% of all new cancers and 2.0% of all cancer deaths [3]. Across countries and subsites, the incidence of head and neck cancer in men exceeds that of women by a factor of 3 to 10.

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Alcohol consumption and tobacco smoking are established risk factors for head and neck cancer [4], while diet may offer protection against this malignancy [4]. Specifically, fruit and vegetable intake was inversely associated with head and neck cancer in several prospective cohort studies[5-9], including the current one [9]. In reviewing the body of epidemiological evidence, the World Cancer Research Fund and the American Institute for Cancer Research concluded that intakes of fruit and non-starchy vegetables *probably* protect against cancers of the mouth, pharynx, and larynx [10].

Fruits and vegetables contain several potential anticarcinogens, including vitamin C, carotenoids/beta-carotene, and dietary fiber [11]. While a number of investigations [12, 13] have examined vitamin C and beta-carotene in relation to head and neck cancer, only a few studies have investigated fiber. Most previous studies of dietary fiber [14, 15] or fiber-rich whole grains [16-23] and cancer of the head and neck had a case-control design, vulnerable to methodological limitations including recall and selection bias. The few prospective studies [5-7] did not examine the risks by fiber subtypes, food source, or head and neck subsites; furthermore, case numbers were small. Therefore, we investigated the role of dietary fiber, total grain, and respective subtypes in relation to head and neck cancer in a large prospective cohort study by anatomic subsites and stratified by sex.

Material and Methods

Study population

The National Institutes of Health (NIH)-AARP Diet and Health Study has been described previously [24]. Briefly, the study recruited men and women by mailing questionnaires to 3.5 million AARP members aged 50-71 years old from six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA and Detroit, MI). Of the 566,402 individuals who returned satisfactorily completed questionnaires and consented to be in the study between 1995 to 1996, we excluded those who had previous cancer at baseline (n=51,234), proxy respondents (n=15,760), and those with box-cox log transformed total energy and total dietary fiber intake of more than two interquartile ranges from the median (n=4,417). The analytical cohort comprised of 494,991 participants (295,312 men and 199,679 women).

Case ascertainment

We identified cancer cases through linkage with 10 state cancer registry databases that included the 8 original states and 2 additional states (Arizona, and Texas) that participants tended to move to during follow-up. Cancers were identified by anatomic site and histologic code of the International Classification of Disease for Oncology (ICD-O, third edition) [25]. Cases were restricted to squamous cell carcinomas. As previously described [26], the total head and neck cancer category included cancers of the oral cavity, oro-hypopharynx, larynx, as well as those overlapping these regions.

Dietary assessment

At baseline, we assessed diet with a self-administered 124-item food-frequency questionnaire (FFQ) that asked about the usual frequency of intake and portion size over the last 12 months, using 10 predefined frequency categories ranging from “never” to “6+ times per day” for beverages, from “never” to “2+ times per day” for solid foods, and 3 categories of portion size. The food items, portion sizes, and nutrient database were based on the method developed by Subar et al [27] using the US Department of Agriculture’s (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals [28]. The nutrient database for dietary fiber was informed by the Association of Official Analytical Chemists method [29]. Over 100 food items contributed to the derivation of total grains, whole grains, and refined

grains. The estimates for whole grains and refined grains were derived using the approach by the MyPyramid equivalent database. This approach assigned a relative proportion of whole grains and refined grains components to each food items depended on sex-specific portion size. A recipe file was used to disaggregate food mixtures into their component ingredients and assigns them to food groups. For analysis, portion sizes of total grains, whole grains, and refined grains, were defined using USDA cup equivalents, e.g. 1 slice of whole grain bread, 1 cup of ready-to-eat whole grain cereal, or ½ cup of cooked whole grain [30].

The FFQ was validated using two nonconsecutive 24-hr dietary recalls in 1,953 participants. The energy-adjusted Pearson correlation coefficients for dietary fiber intake assessed by FFQ and two 24-hour recalls was 0.72 in men and 0.66 in women [31].

Statistical analysis

We used multivariate Cox proportional hazards regression models, after verifying that the proportional hazards assumption was met by modeling the cross-products of time and dietary fiber intake, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) within sex-specific quintiles of intake. Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of cancer diagnosis, death, movement out of the registry areas, or end of follow-up (December 31st, 2006), whichever occurred first. Follow-up time was used as the underlying time metric. Linear trend tests across increasing categories of intake were conducted by assigning participants the median intake for their categories and entering that term as a continuous variable in the regression model.

Dietary fiber intake was adjusted for total energy intake using the residual method [32] while intake of total grains was energy adjusted by the nutrient density method, in which daily intake was expressed as grams per 1000 kcal. All models were adjusted for age (continuous), sex, education (<high school education, completion of high school, some post-high school training, completion of college and completion of graduate school), body mass index (BMI; <18.5, 18.5 to <25, 25 to <30, 30 to <35, and ≥35 kg/m^2), alcohol intake (0, >0-1, 1-3, and >3 drinks/day), smoking dose (never cigarette smoker, quit ≤1 pack/day, quit >1 pack/day, currently smoking ≤1 pack/day, and currently smoking >1 pack/day), vigorous physical activity (never, rarely, 1-3 times/month, 1-2 times/week, 3-4 times/week, 5+ times/week), intake of red meat (quintiles), and total energy (continuous). Further adjustment for intake of fruit and vegetables, vitamin C, folate, beta-carotene, or physical activity at work did not materially alter the results and were not included in the final models.

All analyses were performed stratified by sex. Smoking-stratified models were adjusted for smoking dose and years since smoking cessation where appropriate. To test for interactions, we multiplied the continuous fiber and grain variables by the stratifying variables (sex, smoking status, alcohol consumption) and calculated *p*-interaction using the likelihood ratio test (lrt) with the appropriate degrees of freedom. All analyses were performed using SAS version 9.1. An alpha level of less than 0.05 was considered statistically significant and all tests were two-sided.

Results

During up to 11 years of follow-up, we identified 1,867 cases of head and neck cancer (779 oral cavity, 337 oro-hypopharynx, 622 larynx, and 129 overlapping sites). Men and women reported similar intakes of total fiber and total grains. Men and women in the highest, compared to lowest, quintile of dietary fiber or total grain intake were older, more educated, and were more physically active; furthermore, they tended to have a lower BMI, consumed less alcohol, and less red meat (Table 1). Women in the highest quintile of total fiber and

total grains tended to be never smokers, whereas men were more likely to be former smokers. Dietary fiber and subtypes were not highly correlated with total grain, whole grains, and refined grains (Pearson correlation coefficients <0.40).

We found that sex significantly modified the relation between head and neck cancer and intakes of total fiber (*p*-interaction <0.001), total grains (*p*-interaction = 0.001), and subtypes of fiber (*p*-interactions <0.05); therefore, we presented sex-stratified estimates throughout. Total dietary fiber and grains were inversely associated with head and neck cancers in women; these associations were evident on the continuous scale (total fiber per 10g/day increase: HR = 0.77, 95% CI = 0.64-0.93; total grains per serving/1,000 kcals: HR = 0.89, 95% CI = 0.80-0.99) and when comparing the highest to the lowest quintile of intake (HR_{Q5vsQ1} = 0.61, 95% CI = 0.42-0.89, *p*-trend 0.002; HR_{Q5vsQ1} = 0.73, 95% CI = 0.53-1.02, *p*-trend = 0.040, respectively, Table 2). The inverse association in women was consistent across subtypes of fiber and grains, including whole and refined grains (Table 2) and insoluble and soluble fiber (data not shown); but we did not observe significant dose-dependent trends for fiber from beans (*p*-trend = 0.571).

In men, there was borderline statistically significant association for total fiber and total grains and head and neck cancer on the continuous scale (Table 2); we observed a statistically significant inverse association for fiber from fruits ($HR_{per\ gram/day}$ = 0.89; 95% CI = 0.81-0.97; HR_{Q5vsQ1} = 0.83, 95% CI = 0.69-0.99, *p*-trend = 0.077) and beans ($HR_{per\ gram/day}$ = 0.87; 95% CI = 0.78-0.97; HR_{Q5vsQ1} = 0.82, 95% CI = 0.69-0.96, *p*-trend = 0.012). When examined by anatomic subsites, similar results for intakes of total fiber and total grains were observed, but they did not reach statistical significance (Table 3).

Regardless of sex, there was no effect modification by smoking status (Table 4). We observed statistically significant inverse association with higher intake of total grains for ever drinkers among men, but not for men who did not consume alcohol (Table 4, *p*-interaction = 0.011). No differential effect was observed in this group for total fiber intake. In women, no effect modification was observed for both food groups by alcohol consumption. We also explored effect modification by healthy lifestyle through stratified analyses by levels of physical activity, BMI, and education. We observed no evidence of effect modification by these variables (data not shown).

Discussion

In this prospective cohort study, we found an inverse association between dietary fiber and total grain intake and cancer of the head and neck in women; inverse associations persisted across different subgroups of fiber and grains, including whole and refined grains, and did not differ by subsites. In contrast, the associations were weaker, with borderline statistical significance, in men. Our analyses suggest that the benefit conferred by higher intakes of fiber and total grains may differ by sex.

Three previous prospective studies published on dietary fiber and grain intake in relation to upper aerodigestive tract cancer, which included subsites of head and neck cancer [5-7]. These studies were small (number of cases <95) and reported inconsistent results; furthermore, none comprehensively assessed fiber intake. Cohorts of Japanese [5] and Norwegian [6] men found inverse associations between consumption of bread and upper aerodigestive tract cancers (HR = 0.80; 95% CI = 0.41-1.56 and HR = 0.20; 95% CI = 0.1-0.5, respectively). In the Iowa Women's Health Study, inverse associations were observed for whole grains for both oral/pharyngeal cancers (n = 53, HR = 0.47) and laryngeal cancer (n = 21, HR = 0.44), whereas total fiber consumption was inversely associated with oral/pharyngeal (HR = 0.49) but not laryngeal cancer (HR = 1.82); the

authors did not conduct statistical testing due to small numbers [7], Likewise, the epidemiological evidence from case-control studies on dietary fiber and grain intake is inconsistent [13]. Our findings showing an inverse association between fiber intake and head and neck cancer were similar to some case-control studies [14, 19, 33, 34], but not all [35].

The precise biological mechanism by which dietary fiber and grains might affect head and neck cancer risk is unknown: however, several biological reasons are plausible. Both dietary fiber and grains possess anticarcinogenic properties, which may directly or indirectly confer the protection observed. Dietary fiber scavenges nitrite, a precursor for carcinogenic nitrosoamines [36]. Nitrosoamines are possible risk factors for head and neck cancer [4]. Whole grains are grains in their original form contain three parts: the bran, the germ, and the endosperm [37]. Whole grains are rich in fiber, phytochemicals, antioxidants,and phytoestrogens, and lignans [37-39]. These constituents have been demonstrated to modify cancer risks, including head and neck cancer [4, 20]. Compared to whole grains, refined grains are nutritionally inferior because the milling process substantially reduced the nutrient contents of grains by removing the bran and germ—leaving a largely starchy endosperm. Our finding that refined grains also conferred protection against head and neck cancer does not support the hypothesis that starchy refined grains are risk factors for cancers [14, 40]. It may suggest that other constituents in the endosperm, perhaps residual resistant starch, may play a protective etiologic role. Refined grains are also enriched with B vitamins (riboflavin, niacin, thiamin and iron) [41]. Nevertheless, it is speculative at best to attribute any of these constituents to the protection observed for refined grains in our study and additional research is warranted.

Our results may also be partly attributed to nutrients or micronutrients inherent in fruits and vegetables. Freedman et al previously showed that intake of fruits and vegetables was associated with a reduced risk of head and neck cancers in the same population [9]. In additional analyses, we further adjusted for intakes of fruits, vegetables, folate, beta-carotene, and vitamin C. The observed inverse associations changed only slightly, suggesting that other dietary components found in fruits and vegetables do not fully explain the protective effect of dietary fiber and grains observed.

Alternatively, fiber and grain intake is associated with aspects of a healthy lifestyle, such as a lower propensity to smoke cigarettes and consume alcohol, lower BMI, and higher physical activity; as such unmeasured or poorly measured exposures could affect our results. Although we took great care to adjust for these confounders in our analyses, we cannot exclude the possibility of residual confounding affecting our results. In particular, cigarette smoking is a significant risk factor for head and neck cancer. Risk estimates for total fiber and total grains were attenuated in never smokers.

Despite similar reported median intakes of fiber and grains in the sex-specific quintiles, the observed sex-specific benefit merits further discussion. Head and neck cancer is considerably more common among men than women [4]. The sex-ratios range from 3 to 10 by anatomic subsite and can further vary within particular subsites, such as the larynx [2]. Tobacco exposure and alcohol consumption, both established risk factors for head and neck cancer, likely do not explain these differences as elevated incidence rates in men relative to women persisted in never smokers who did not drink alcohol in the NIH-AARP Diet and Health Study [26, 42]. The accumulating evidence led some investigators to postulate a possible role of estrogen and hormone-related factors in the etiology of head and neck cancer [43-46]. Recent findings from the NIH-AARP Diet and Health Study showed that menopausal hormone therapy (MHT) was inversely associated with incident squamous cell carcinomas, which included head and neck cancer [46]. Currently, it is unclear whether there is a role for dietary fiber and grains in hormone-related head and neck cancer, although

dietary fiber and whole grains have been shown to reduce endogenous estrogen levels [47, 48]. In our analyses, additional adjustment for MHT and age at menopause did not affect the results.

The present study has several strengths. To our knowledge, it is the largest prospective cohort study to investigate the role of dietary fiber, grains, and their respective subtypes in relation to head and neck cancer, and first to report estimates across subsites within this group of malignancies. Furthermore, the relatively large number of head and neck cancers permitted assessment of sex-specific associations with dietary fiber and grain intake. The study benefits from a wide range of dietary fiber intake and detailed information on tobacco exposure and alcohol consumption, which allowed careful adjustment for these two important risk factors.

Limitations include the lack of information on human papillomavirus (HPV) infection, which is a risk factor for specific head and neck cancer subsites [49]. We investigated multiple subtypes of fiber, grains, and subsites of head and neck cancer; therefore, it is possible that our results might be due to chance. Additionally, we lack information on smoking duration and passive smoke exposure, which could possibly confound the observed relation. Although our study is the largest to date to examine the role of fiber and grains in relation to head and neck cancer, we are still limited by a modest numbers of cases, particularly for subgroup analyses.

In conclusion, total fiber and grains were inversely associated with head and neck cancers in this prospective cohort study. We observed a more pronounced benefit with intake of total fiber and grains among women compared to men. Our findings suggest a role of fiber and grains in the etiology of head and neck cancer.

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Table 1

Selected characteristics by sex-specific quintiles of dietary fiber intake and grains intake, NIH-AARP Diet and Health Study (1995-2006)

	Quintiles of total fiber						Quintiles of total grains					
	Women			Men			Women			Men		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Total fiber (g/d)*	13.3	19	28	11.3	18.1	27.8	17	19	20.5	14.9	18.1	20.7
Total grain (servings/1,000 kcal)*	2.4	3.0	3.1	2.3	2.9	3.2	1.7	2.9	4.2	1.7	2.8	4.1
Age (mean years)	61.1	62	62.2	61.3	62.3	62.6	61.8	61.9	61.9	62	62.7	63.1
BMI (kg/m^2)	25.9	25.8	25.1	27.1	26.7	26.1	25.6	25.8	25.6	27	26.7	26.2
Education (%)												
Less than high school	8.3	5.6	5.6	7.4	5.4	5.4	7.4	5.7	6.3	6.8	5.2	6.1
12 years (completed high school)	30.1	25.1	21.1	19.2	15.0	13.3	25.9	25.7	24.5	17.4	15.0	14.9
Some post-high school training	35.6	35.6	34.6	33.9	31.6	28.9	36.2	35.3	34.5	33.9	31.4	29.3
Completed college	12.6	15.2	16.0	20.4	22.1	21.4	13.4	14.9	15.4	20.1	22.4	21.7
Completed graduate school	10.0	15.4	19.0	16.5	23.5	28.2	12.7	15.3	16.5	18.6	23.6	25.5
Cigarette smoking status (%)												
Never	35.5	46.0	48.3	21.8	30.0	34.4	38.9	45.0	46.4	22.9	30.5	32.4
Former	30.4	37.4	39.2	49.2	56.5	56.2	32.9	37.1	39.4	53.0	54.9	56.1
Current	30.4	13.3	8.5	25.0	9.6	5.3	23.8	14.6	11.9	19.4	10.8	7.7
Vigorous physical activity (%)[1]												
Never	10.2	4.9	3.6	5.8	3.0	2.3	7.1	5.3	5.9	4.6	3.1	3.5
Rarely	24.43	15.9	10.2	17.2	10.9	6.8	18.0	16.3	16.1	13.8	11.0	10.5
1-3 times/month	17.3	14.9	9.8	16.9	13.3	8.4	14.7	14.3	13.7	14.5	13.1	11.5
1-2 times/week	20	22.3	18.8	22.9	23.2	17.5	19.9	21.8	20.2	21.8	22.7	20.1
3-4 times/week	16.7	25.8	30.8	21.3	29.3	32	22.3	25.6	16.1	24.8	28.5	29.6
5 or more times/week	9.9	15.1	25.5	15.0	19.3	32.1	16.2	15.6	16.8	19.3	20.8	23.9
Alcohol intake (%)												
0 drink/day	26.7	28.0	34.3	18.1	19.8	25.0	26.7	27.7	34.6	14.9	20.0	27.3
>0 to 1 drink/day	50.6	60.5	57.0	40.3	53.0	52.3	50.1	59.8	59.2	34.4	52.7	58.4
1 to 3 drinks/day	13.6	9.7	7.4	17.7	19.1	17.2	14	10.7	5.5	19.3	20.9	12.5
>3 drinks/day	8.5	1.2	0.7	23.7	7.8	5.2	6.5	1.4	0.3	31.1	6.1	1.4

	Quintiles of total fiber						Quintiles of total grains					
	Women			Men			Women			Men		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Total daily calories*,a	1577	1328	1692	2214	1679	2024	1469	1487	1384	2028	1885	1713
Total fruit intake *,b	0.9	1.8	2.5	0.7	1.4	2.1	1.9	1.7	1.5	1.2	1.4	1.3
Total vegetable intake*,b	1.4	2.3	3.4	1.2	1.9	2.8	2.2	2.3	2.1	1.7	1.9	1.9
Red meat intake *,b	34.4	27.3	16.3	44.1	36.4	23.1	26.5	28.4	21.4	36.2	37.8	27.4

*Median intake;

*a*kcal//d;

*b*servings/1,00 0kcal

*1*Numbers/percentage might not add to 100% due to missing data

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Table 2

Sex-specific multivariate hazard ratios (HR) [1] and 95% confidence intervals (CI) for subtypes of dietary fiber and grain intakes and head and neck cancer, NIH-AARP Diet and Health Study (1995-2006)

Category[2]	Women							Men						*p*-trend	*p*-interaction[3]
	Continuous[c]	Q1	Q2	Q3	Q4	Q5	p-trend	Continuous[c]	Q1	Q2	Q3	Q4	Q5		
Total fiber[a]															
N_{cases}		155	87	64	50	45			448	294	280	211	233		
HR	0.77	1.00	0.86	0.74	0.63	0.61	0.0020	0.93	1.0	0.90	0.97	0.78	0.88	0.079	<0.001
95% CI	0.64-0.93	ref	0.65-1.14	0.54-1.01	0.45-0.89	0.42-0.89		0.86-1.00	ref	0.78-1.05	0.83-1.14	0.66-0.93	0.73-1.05		
Total grains[b]															
N_{cases}		136	81	68	60	56			414	327	248	239	238		
HR	0.89	1.0	0.76	0.74	0.72	0.73	0.040	0.95	1.0	0.99	0.84	0.86	0.91	0.145	0.0010
95% CI	0.80-0.99	ref	0.57-1.00	0.55-1.00	0.52-0.98	0.53-1.02		0.89-1.00	ref	0.85-1.15	0.71-0.99	0.72-1.03	0.76-1.09		
Whole grains[b]															
N_{cases}		139	89	65	49	59			419	292	267	255	233		
HR	0.84	1.00	0.82	0.66	0.54	0.71	0.0050	0.94	1.00	0.87	0.87	0.89	0.85	0.139	0.047
95% CI	0.64-1.11	ref	0.62-1.07	0.49-0.89	0.39-0.75	0.51-0.97		0.82-1.07	ref	0.74-1.01	0.75-1.02	0.76-1.05	0.72-1.01		
Refined grains[b]															
N_{cases}		123	77	82	63	56			398	317	263	244	244		
HR	0.85	1.00	0.74	0.89	0.73	0.69	0.027	0.93	1.00	0.96	0.86	0.84	0.87	0.047	0.017
95% CI	0.75-0.97	ref	0.56-0.99	0.66-1.18	0.53-1.00	0.49-0.95		0.87-1.00	ref	0.83-1.12	0.73-1.02	0.71-1.00	0.73-1.04		
Fiber from grains[a]															
N_{cases}		137	84	75	50	55			396	263	280	263	264		
HR	0.77	1.00	0.81	0.80	0.57	0.66	0.0030	0.97	1.00	0.84	0.95	0.93	0.95	0.915	0.0010
95% CI	0.63-0.95	ref	0.61-1.07	0.60-1.07	0.41-0.80	0.47-0.91		0.90-1.05	ref	0.71-0.98	0.81-1.17	0.80-1.10	0.81-1.12		
Fiber from fruits[a]															
N_{cases}		140	96	74	50	41			448	285	266	251	216		
HR	0.75	1.00	1.02	0.89	0.67	0.59	0.0010	0.89	1.00	0.90	0.93	0.94	0.83	0.077	0.0010
95% CI	0.61-0.92)	ref	0.78-1.33	0.66-1.19	0.48-0.94	0.40-0.85		0.81-0.97	ref	0.77-1.10	0.79-1.10	0.79-1.11	0.69-0.99		
Fiber from vegetables[a]															

Category[2]	Women							Men						*p*-trend	*p*-interaction[3]
	Continuous[c]	Q1	Q2	Q3	Q4	Q5	p-trend	Continuous[c]	Q1	Q2	Q3	Q4	Q5		
N_{cases}		114	89	72	70	56			405	294	262	252	253		
HR	0.91	1.00	0.99	0.87	0.88	0.72	0.038	0.95	1.00	0.96	0.91	0.90	0.91	0.193	0.14
95% CI	0.78-1.06	ref	0.74-1.31	0.64-1.17	0.65-1.19	0.52-1.00		0.88-1.02	ref	0.82-1.12	0.77-1.07	0.76-1.06	0.77-1.07		
Fiber from beans[a]															
N_{cases}		98	80	75	82	64			379	281	301	258	247		
HR	0.83	1.00	0.99	0.99	1.08	0.90	0.57	0.87	1.00	0.91	1.05	0.89	0.82	0.012	0.095
95% CI	0.62-1.18	ref	0.72-1.35	0.71-1.37	0.78-1.50	0.65-1.24		0.78-0.97	ref	0.78-1.35	0.89-1.24	0.75-1.05	0.69-0.96		

[a] gram per day;

[b] serving per1,000 kcal ;

[c] per 10gram/day increase or per serving/1000kcal increase

[1] Adjusted for age at entry, education, body mass index, physical activity, alcohol intake, cigarette-smoke-dose, red meat intake, total energy intake. In analyses of total fiber and grains, these variables were mutually adjusted.

[2] Median intake per sex-specific quintile for Q1, Q3, and Q5 (Female/Male)

Total dietary fiber [a] — 13.33/11.34, 18.98/18.06, 27.96/27.77; Total dietary grain[b] — 1.72/1.70, 2.86/2.35, 4.23/4.15 ; Total fiber from grain [a] — 3.33/2.99, 5.55/5.78, 9.38/10.47;

Total whole grains[b] — 0.15/0.12 , 0.49/0.47, 1.10/1.10; Total refined grain[b] —1.37/1.36, 2.28/2.25, 3.43/3.36; Total fiber from fruits[b] —1.47/0.73, 3.86/3.21, 8.31/7.78;

Total fiber from vegetables[b] —3.74/2.68, 6.24/5.52, 11.04/10.07; Total fiber from beans[b] —0.57/0.24, 1.72/1.75, 3.69/4.60

[3] Based on likelihood-ratio-test, *p*-interaction by sex

Table 3

Sex-specific multivariate hazard ratios (HR) [1] and 95% confidence intervals (CI) for dietary fiber and grains intakes and subsites of head and neck cancer, NIH-AARP Diet and Health Study (1995-2006)

Subsites Category	Women						Men					
	Q1	Q2	Q3	Q4	Q5	*p*-trend	Q1	Q2	Q3	Q4	Q5	*p*-trend
Oral Cavity												
Total fiber[a]												
N_{cases}	76	39	38	29	25		153	123	112	82	102	
HR	1.00	0.74	0.82	0.67	0.62	0.055	1.00	1.07	1.06	0.81	0.99	0.576
(95% CI)	(ref)	(0.49-1.11)	(0.54-1.25)	(0.42-1.07)	(0.37-1.03)		(ref)	(0.83-1.40)	(0.82-1.38)	(0.60-1.08)	(0.75-1.32)	
Total grains[b]												
N_{cases}	69	42	30	36	30		148	134	97	97	96	
HR	1.00	0.74	0.60	0.78	0.71	0.153	1.00	1.11	0.87	0.92	0.95	0.421
(95% CI)	(ref)	(0.50-1.10)	(0.39-0.94)	(0.51-1.20)	(0.45-1.13)		(ref)	(0.87-1.41)	(0.67-1.15)	(0.69-1.21)	(0.71-1.26)	
Oro-hypopharynx												
Total fiber[a]												
N_{cases}	26	22	11	7	8		96	53	42	40	32	
HR	1.00	1.33	0.82	0.59	0.75	0.239	1.00	0.82	0.76	0.79	0.66	0.071
(95% CI)	(ref)	(0.73-2.43)	(0.39-1.73)	(0.24-1.43)	(0.31-1.80)		(ref)	(0.58-1.16)	(0.51-1.11)	(0.53-1.18)	(0.42-1.04)	
Total grains[b]												
N_{cases}	26	17	17	7	7		93	96	40	45	39	
HR	1.00	0.84	0.94	0.43	0.45	0.031	1.00	0.67	0.69	0.86	0.82	0.508
(95% CI)	(ref)	(0.45-1.57)	(0.50-1.79)	(0.18-1.01)	(0.19-1.09)		(ref)	(0.47-0.97)	(0.46-1.02)	(0.58-1.27)	(0.54-1.26)	
Larynx												
Total fiber[a]												
N_{cases}	43	21	12	13	7		167	101	105	75	78	
HR	1.00	0.81	0.60	0.73	0.47	0.058	1.00	0.84	1.02	0.80	0.88	0.345
(95% CI)	(ref)	(0.47-1.39)	(0.29-1.11)	(0.37-1.41)	(0.20-1.10)		(ref)	(0.65-1.09)	(0.78-1.32)	(0.59-1.07)	(0.65-1.19)	
Total grains[b]												
N_{cases}	30	17	18	14	17	0.452	146	120	97	84	84	0.749

Subsites Category	Women						Men					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p*-trend**
HR	1.00	0.79	1.05	0.93	1.27		1.00	1.08	0.99	0.93	1.00	
(95% CI)	(ref)	(0.43-1.45)	(0.57-1.93)	(0.48-1.81)	(0.67-2.41)		(ref)	(0.84-1.39)	(0.75-1.31)	(0.69-1.24)	(0.74-1.36)	

[a] gram per day;

[b] serving per1,000 kcal

[1] Adjusted for age at entry, education, body mass index, physical activity, alcohol intake, cigarette-smoke-dose, red meat intake, total energy intake. In analyses of total fiber and total grains, the variables are mutually adjusted for the other.

Table 4

Sex-specific multivariate hazard ratios (HR) and 95% confidence intervals (CI) for dietary fiber and grain intakes and head and neck cancer in NIH-AARP Diet and Health Study (1995-2003), stratified by smoking status and alcohol consumption

	Overall N_{cases} (F/M) [a]	Total fiber				Total grains			
		Women		Men		Women		Men	
		HR[b]	95% CI	HR[b]	95% CI	HR[c]	95% CI	HR[c]	95% CI
Whole cohort	401/1466	0.77	0.64-0.93	0.93	0.86-1.00	0.89	0.80-0.99	0.95	0.89-1.00
Smoking status									
Never smokers	70/237	0.89	0.59-1.35	1.03	0.85-1.25	1.08	0.85-1.38	0.95	0.82-1.10
Former smokers	113/690	0.73	0.51-1.04	0.94	0.84-1.05	0.88	0.72-1.08	0.99	0.91-1.08
Current smokers	201/473	0.83	0.63-1.08	0.92	0.80-1.05	0.82	0.70-0.97	0.94	0.84-1.05
		p-interaction[2]=0.63		*p*-interaction[2]=0.41		*p*-interaction[2]=0.079		*p*-interaction[2]=0.16	
Alcohol consumption									
Never	112/327	0.78	0.57-1.07	0.91	0.78-1.06	0.94	0.78-1.14	1.09	0.98-1.22
Ever	212/755	0.70	0.53-0.92	0.95	0.85-1.06	0.77	0.65-0.91	0.91	0.83-0.99
		p-interaction[2] = 0.41		*p*-interaction[2] = 0.87		p-interaction[2] = 0.37		*p*-interaction[2] = 0.011	

[a] F/M: Female/Male

[b] Continuous variable, 10 grams per day increase

[c] Continuous variable, serving per1,000 kcal increase

[1] Adjusted for age at entry, education, body mass index, physical activity, cigarette-smoke-dose (former and current smokers), red meat intake, and total energy intake. In analyses for total fiber and total grains, the variables are mutually adjusted for the other.

[2] *p*-interaction, based on likelihood-ratio-test