Index-based dietary patterns and risk of head and neck cancer in a large prospective study1–4

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ABSTRACT
Background: Head and neck cancer (HNC) is the seventh most common cancer worldwide. Although diet has been proposed to play an important role in HNC, few associations with diet have been convincing other than alcohol intake. Studies of dietary patterns that examine overall diets may provide broader insight than studies of individual foods. Little is known about the association between dietary patterns and risk of HNC.

Objective: We prospectively evaluated the association between 2 index-based dietary patterns [ie, the Healthy Eating Index-2005 (HEI-2005) and alternate Mediterranean Diet Score (aMED)] and risk of head and neck squamous cell carcinoma.

Design: We included 494,967 participants from the NIH-AARP Diet and Health study (1995-2006). HRs (95% CIs) were estimated by using Cox regression. Scores for the HEI-2005 and aMED were calculated on the basis of diet assessed by using a baseline food-frequency questionnaire. Higher scores reflected adherence to dietary recommendations for healthy eating. Our main outcome was the incidence of HNC, including cancer of the larynx, oral cavity, and oropharynx.

Results: A total of 1868 HNC cases were identified during follow-up. Higher HEI-2005 scores were associated with reduced risk of HNC in men [HR: 0.74 (95% CI: 0.61, 0.89) for highest compared with lowest quintiles; P-trend = 0.0008] and women [HR: 0.48; 95% CI: 0.33, 0.70; P-trend < 0.0001]. High aMED scores were also associated with lower HNC risk in men (HR: 0.80; 95% CI: 0.64, 1.01; P-trend = 0.002) and women (HR: 0.42; 95% CI: 0.24, 0.74; P-trend < 0.0001). Associations were similar among subsites. We did not find significant interactions between smoking and alcohol intake and each index on HNC risk.

Conclusions: HEI-2005 and aMED scores were associated inversely with risk of HNC. Large interventional studies are required to assess the causality before conveying definite public health messages. This trial was registered at clinicaltrials.gov as NCT00340015. Am J Clin Nutr 2014;99:559–66.

INTRODUCTION

Head and neck cancer (HNC)5, which encompasses cancers in the oral cavity, oropharynx, hypopharynx, and larynx, is the seventh most common cancer worldwide, and only 40–50% of cases will survive for 5 y (1). In the United States, ~53,640 new cases of HNC will be diagnosed in 2013, and the incidence is 3-fold higher in men than women (2).

Compelling evidence has indicated that smoking and alcohol intake are risk factors for HNC (3–6). Infection with high-risk types of human papillomavirus (HPV) has been correlated with some cancers of the oropharynx and oral cavity, particularly those in the tonsils and base of the tongue (7). Diet has also been proposed to play an important role (8, 9), but few associations with diet have been convincing other than alcohol intake. Several prospective studies have suggested inverse associations with fruit and vegetable intake (9, 10), particularly for fruit and vegetables that are rich in carotenoids (9). The role of other dietary items in HNC has rarely been addressed.

In contrast to individual foods and nutrients, dietary patterns represent a broader picture of food and nutrient consumption (11, 12). An adherence to index-based dietary patterns, which were developed according to established dietary guidelines, has been shown to reduce risk of total mortality and the development of several individual cancers in prospective studies (13–17). However, few studies have investigated the association between index-based dietary patterns and HNC risk (18, 19). Existing studies have focused on the traditional Mediterranean diet score (18, 19) and were limited by using a retrospective study design, which could have possibly been affected by selection and recall biases. In the current study, we prospectively evaluated the association between the Healthy Eating Index-2005 (HEI-2005), which reflects 2005 Dietary Guidelines for Americans (20), and the alternate Mediterranean Diet Score (aMED), which adapts the principles of the traditional Mediterranean diet to the American population (11, 21), and risk of developing HNC in the NIH-AARP Diet and Health Study, which includes a large cohort in the United States.

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4Address reprint requests and correspondence to W-Q Li, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850. E-mail: liw9@mail.nih.gov.
5Abbreviations used: aMED, alternate Mediterranean Diet Score; HEI-2005, Healthy Eating Index-2005; HNC, head and neck cancer; HPV, human papillomavirus; SoFAAS, solid fat, alcohol, and added sugar.

Supplemental Material can be found at: http://ajcn.nutrition.org/content/suppl/2014/02/14/ajcn.113.073163.DCSupplemental.html

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SUBJECTS AND METHODS

Study population

Study participants enrolled in the NIH-AARP Diet and Health Study (www.clinicaltrials.gov; NCT00340015) in 1995–1996. A total of 566,398 AARP members aged 50–71 y residing in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI) completed a questionnaire that inquired about their demographic characteristics, diet, and lifestyle practices. We excluded proxy respondents (n = 15,760), participants with prevalent cancer at baseline (n = 51,234), and those with an implausible total energy intake (>2 times the IQR of sex-specific Box-Cox log-transformed intake) (n = 4417), and 0 person-years of follow-up (n = 20). A total of 494,967 participants, including 295,299 men and 199,668 women, were included in our analyses. The study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute. We considered questionnaire completion and return to imply written informed consent.

Assessment of diet-quality indexes

At baseline, participants reported their frequencies of intake and portion sizes over the past year by using a 124-item food-frequency questionnaire, which defined 10 response categories that ranged from never to ≥2 times/d for solid foods and never to ≥6 times/d for beverages (22). Food items, portion sizes, and nutrient databases were constructed on the basis of data from the 1994–1996 USDA's Continuing Survey of Food Intakes by Individuals (23). The food-frequency questionnaire was validated by using 2 nonconsecutive 24-h dietary recalls in a subset of study participants; correlation coefficients ranged from 0.36 to 0.76 for nutrients and 0.35 to 0.84 for food groups (24, 25).

The HEI-2005 was designed to assess compliance with the 2005 Dietary Guidelines for Americans (20), with 12 components for a maximum of 100 points (optimal adherence). Six components (total grains, whole grains, total vegetables, dark-green and orange vegetables and legumes, total fruit, and whole fruit) were awarded 0–5 points. Five components (milk, meat and beans, oils, saturated fat, and sodium) were worth 0–10 points. The component of calories from solid fat, alcohol, and added sugar (SoFAAS) was awarded 0–20 points. Components and scoring standards were measured by using the density per 1000 kcal. Higher scores indicate lower intakes of components of saturated fat, sodium, and calories from SoFAAS but indicated higher intakes of other components.

The aMED was modified from the original Mediterranean diet score to adapt to an American population (11, 21) to evaluate 9 components with a maximum score of 9 (optimal adherence). Components were energy adjusted and standardized to 2500 cal for men and 2000 cal for women. Participants received one point for an intake above the sex-specific median for 7 components, including vegetables (excluding potatoes), legumes, fruit, nuts, whole grains, fish, and the ratio of mono-unsaturated to saturated fat and one point for red and processed meat intake below the median. Otherwise, a score of zero was awarded. For alcohol, one point was given for a moderate alcohol intake (5–15 g/d). For other intakes of alcohol, a score of zero was awarded.

Cohort follow-up and assessment of HNC

Participants were followed from 1995 to 1996 through 31 December 2006. Addresses were updated periodically by matching to the National Change of Address database maintained by the US Postal Service. Vital status was ascertained by periodic linkage to the Social Security Administration Death Master File, linkage with cancer registries, questionnaire responses, and responses to other mailings. Incident cancer cases were identified by linkage of the cohort to state cancer-registry databases, which had a minimum sensitivity of ~90% for cancer case ascertainment (26). Cancer sites were determined by the anatomic site and histologic code of the International Classification of Disease for Oncology, third edition. The overall HNC included cancers of the oral cavity (C00.1–C06.9), oropharynx (C09.0–C10.9, C12.9–C14.0), larynx (C32.0–32.9), and those that overlapped regions and were restricted to squamous cell carcinomas (histology code 8050–8076). 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 oropharynx included tumors in the tonsil (C09.0–C09.9), oropharynx (C10.0–C10.9), pyriform sinus (C12.9), hypopharynx (C13.0–C13.9), and pharynx not otherwise specified (C14.0).

Statistical analysis

Person-years for each participant were calculated from the study baseline (1995–1996) through the occurrence of the main outcome, date of death, movement out of study areas, or end of follow-up (31 December 2006), whichever came first. HEI-2005 scores were categorized into quintiles, and aMED scores were classified into 5 categories (0–2, 3, 4, 5–6, and 7–9). Cox proportional hazards models were used to calculate age-adjusted and multivariate-adjusted HRs and 95% CIs. Multivariate analyses were adjusted for age, race or ethnic groups, smoking [never, former (≤1 or >1 pack/d), or current (≤1 or >1 pack/d)], alcohol intake (0, >0–1, >1–3, or >3 drinks/d), education, BMI, usual activity throughout the day, vigorous physical activity, and total energy intake. An indicator was created for missing data of each covariate. We conducted a sensitivity analysis by adjusting for more-detailed categories of smoking use, including information about the time since quitting and cigarettes per day in more-detailed categories. Results after this additional adjustment did not materially change. We tested the heterogeneity in effect estimates between men and women and between subsites by using the Q statistic. Because of significant differences in associations between men and women, we chose to present sex-specific results. Tests for the linear trend across categories of an index were performed by assigning the median score to each category and modeling this value as a continuous variable. A component analysis in a given index was conducted by adjusting for the modified total score with the exclusion of each component. In secondary analyses, we evaluated the trend in HNC risk associated with each index by subgroups of smoking, alcohol intake, and education.

We tested the proportional hazards assumption by including an interaction term between person-years and each index (P > 0.05 for all tests). To minimize a reverse-causality bias, a lag analysis
was conducted by excluding outcomes that occurred within the first 2 y of follow-up. Interactions between subgroups of smoking, alcohol intake, and education and each index were tested by using likelihood-ratio tests. Several additional sensitivity analyses were conducted. Because alcohol intake is an established risk factor for HNC, we examined associations between HNC and modified dietary indexes by excluding the alcohol component from scores. We also modified the aMED by awarding one point for no alcohol intake. We adjusted for age at menopause and postmenopausal hormone therapy in women because of the previous report that suggested an association between these factors and cancers of the upper gastrointestinal tract (2). Other sensitivity analyses were conducted by excluding individuals with prevalent type 2 diabetes or cardiovascular disease or those who reported a poor or fair health status at baseline because subjects with these diseases may have changed their dietary patterns. All statistical tests were performed with SAS 9.2 software (SAS Institute Inc).

RESULTS

Baseline characteristics of study participants are reported in Table 1. The mean (±SD) age at baseline was 62.1 ± 5.3 y in men and 61.9 ± 5.4 y in women. Participants with a higher score on the HEI-2005 or aMED were older and less likely to smoke, drink alcohol, or perform heavy work. These subjects also tended to be physically active, have a higher educational level, and report a lower intake of total calories.

We documented a total of 1466 HNC cases over 2,838,422 person-years in men and 402 cases over 1,964,936 person-years in women. In age-adjusted analysis, scores of the HEI-2005 and aMED were monotonically associated with reduced risk of HNC in both sexes (P-trend < 0.0001). The associations were attenuated after we controlled for covariates, particularly for smoking and alcohol intake, but remained monotonic and significant (Table 2). Compared with HEI-2005 scores in the lowest quintile, the HR (95% CI) for the highest quintile was 0.74 (0.61, 0.89) in men (P-trend = 0.0008) and 0.48 (0.33, 0.70) in women (P-trend < 0.0001). HNC risk decreased with increasing aMED score in men [HR: 0.80 (95% CI: 0.64, 1.01) for a score from 7 to 9 compared with from 0 to 2; P-trend = 0.002] and women (HR: 0.42; 95% CI: 0.24, 0.74; P-trend < 0.0001). Associations were significantly different between men and women, and P-heterogeneity was 0.048 for the HEI-2005 and 0.039 for the aMED.

During the follow-up, we identified 526 cancers of the larynx, 572 cancers of the oral cavity, and 263 cancers of the oropharynx in men and 96 cancers of the larynx, 208 cancers of the oral cavity, and 74 cancers of the oropharynx in women. The association of oral cavity cancer with both the HEI-2005 and aMED was not significant in men. However, HRs for subsites were consistently <1. We did not find heterogeneity in effect estimates for cancers of the oral cavity, larynx, and oropharynx (Table 3). P-heterogeneity was 0.29 in men and 0.46 in women for the HEI-2005 and 0.52 in men and 0.68 in women for the aMED.

Associations were similar after the exclusion of outcomes that occurred within the first 2 y of follow-up (all P-trend < 0.05). For

TABLE 1

Baseline characteristics of study participants by the sex-specific distribution of diet-index scores in the NIH-AARP Diet and Health Study (295,299 men and 199,668 women)

<table>
<thead>
<tr>
<th></th>
<th>Healthy Eating Index-2005</th>
<th>Alternate Mediterranean Diet Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quintile 1</td>
<td>Quintile 3</td>
</tr>
<tr>
<td>Men n</td>
<td>59,059</td>
<td>59,060</td>
</tr>
<tr>
<td>Score</td>
<td>78</td>
<td>67</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.5 ± 5.41</td>
<td>62.2 ± 5.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 ± 4.3</td>
<td>27.4 ± 4.2</td>
</tr>
<tr>
<td>Race (non-Hispanic white) (%)</td>
<td>94.3</td>
<td>93.4</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>24.0</td>
<td>8.3</td>
</tr>
<tr>
<td>Alcohol intake (&gt;3 drinks/d) (%)</td>
<td>32.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Usual activity (heavy work) (%)</td>
<td>5.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Physical activity (≥5 times/wk) (%)</td>
<td>15.7</td>
<td>20.7</td>
</tr>
<tr>
<td>Education (college graduate) (%)</td>
<td>34.5</td>
<td>46.9</td>
</tr>
<tr>
<td>Total calories (kcal/d)</td>
<td>2369 ± 1046</td>
<td>1964 ± 779</td>
</tr>
<tr>
<td>Women n</td>
<td>39,933</td>
<td>39,934</td>
</tr>
<tr>
<td>Score</td>
<td>54</td>
<td>71</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.2 ± 5.5</td>
<td>61.8 ± 5.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 6.1</td>
<td>26.8 ± 5.6</td>
</tr>
<tr>
<td>Race (non-Hispanic white) (%)</td>
<td>91.0</td>
<td>90.6</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>29.0</td>
<td>11.8</td>
</tr>
<tr>
<td>Alcohol intake (&gt;3 drinks/d) (%)</td>
<td>9.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Usual activity (heavy work) (%)</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Physical activity (≥5 times/wk) (%)</td>
<td>10.7</td>
<td>16.9</td>
</tr>
<tr>
<td>Education (college graduate) (%)</td>
<td>22.5</td>
<td>32.0</td>
</tr>
<tr>
<td>Total calories (kcal/d)</td>
<td>1727 ± 774</td>
<td>1544 ± 640</td>
</tr>
</tbody>
</table>

1 All values are medians.
2 Mean ± SD (all such values).
example, the HR (95% CI) for the highest compared with lowest categories was 0.75 (0.61, 0.92) for the HEI-2005 in men, 0.51 (0.34, 0.77) for the HEI-2005 in women, 0.84 (0.66, 1.08) for the aMED in men, and 0.48 (0.27, 0.87) for the aMED in women. Modification of the aMED by assigning one point for no alcohol intake did not appreciably change results. In other sensitivity analyses, additional adjustment for age at menopause and postmenopausal hormone therapy for women, with the exclusion of individuals who reported type 2 diabetes or heart disease at baseline or those who reported an unfavorable health status did not materially affect results (data not shown).

### TABLE 2

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEI-2005 (quintiles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men Cases (n)</td>
<td>498</td>
<td>299</td>
<td>221</td>
<td>245</td>
<td>203</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.58 (0.51, 0.67)</td>
<td>0.42 (0.36, 0.50)</td>
<td>0.47 (0.40, 0.54)</td>
<td>0.38 (0.32, 0.45)</td>
</tr>
<tr>
<td>Women Cases (n)</td>
<td>157</td>
<td>107</td>
<td>54</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.66 (0.52, 0.84)</td>
<td>0.33 (0.24, 0.45)</td>
<td>0.27 (0.20, 0.38)</td>
<td>0.23 (0.16, 0.33)</td>
</tr>
</tbody>
</table>

aMED (scores) 0–2 3 4 5–6 7–9 —

Men Cases (n) 397 297 309 363 100 —

HR (95% CI) 1.00 0.75 (0.64, 0.87) 0.65 (0.56, 0.76) 0.48 (0.42, 0.55) 0.44 (0.35, 0.55) 0.0001

Women Cases (n) 127 92 83 86 14 —

HR (95% CI) 1.00 0.63 (0.48, 0.83) 0.47 (0.36, 0.63) 0.33 (0.25, 0.43) 0.23 (0.13, 0.39) 0.0001

### TABLE 3

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEI-2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men Larynx</td>
<td>187</td>
<td>1.00</td>
<td>95</td>
<td>0.70 (0.54, 0.91)</td>
<td>82</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>172</td>
<td>1.00</td>
<td>120</td>
<td>0.91 (0.72, 1.17)</td>
<td>93</td>
</tr>
<tr>
<td>Orohypopharynx</td>
<td>105</td>
<td>1.00</td>
<td>60</td>
<td>0.82 (0.59, 1.14)</td>
<td>29</td>
</tr>
<tr>
<td>Women Larynx</td>
<td>46</td>
<td>1.00</td>
<td>27</td>
<td>0.92 (0.56, 1.51)</td>
<td>12</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>73</td>
<td>1.00</td>
<td>53</td>
<td>0.97 (0.67, 1.41)</td>
<td>33</td>
</tr>
<tr>
<td>Orohypopharynx</td>
<td>30</td>
<td>1.00</td>
<td>19</td>
<td>0.90 (0.49, 1.63)</td>
<td>5</td>
</tr>
</tbody>
</table>

aMED | | | | | |

Men Larynx | 149 | 1.00 | 107 | 0.89 (0.69, 1.14) | 97 | 0.78 (0.60, 1.02) | 144 | 0.86 (0.67, 1.10) | 29 | 0.68 (0.45, 1.03) | 0.059 |
| Oral cavity | 128 | 1.00 | 118 | 1.10 (0.86, 1.42) | 141 | 1.24 (0.97, 1.58) | 142 | 0.86 (0.67, 1.12) | 43 | 0.95 (0.66, 1.37) | 0.31 |
| Orohypopharynx | 88 | 1.00 | 53 | 0.77 (0.54, 1.08) | 52 | 0.75 (0.52, 1.06) | 50 | 0.54 (0.38, 0.79) | 20 | 0.91 (0.54, 1.52) | 0.046 |
| Women Larynx | 28 | 1.00 | 28 | 1.18 (0.69, 2.00) | 20 | 0.85 (0.47, 1.54) | 17 | 0.61 (0.33, 1.15) | 3 | 0.59 (0.18, 2.01) | 0.075 |
| Oral cavity | 70 | 1.00 | 48 | 0.71 (0.49, 1.03) | 37 | 0.50 (0.33, 0.75) | 43 | 0.43 (0.29, 0.64) | 10 | 0.47 (0.24, 0.93) | <0.0001 |
| Orohypopharynx | 22 | 1.00 | 13 | 0.65 (0.32, 1.29) | 21 | 1.00 (0.54, 1.84) | 18 | 0.68 (0.35, 1.32) | 0 | N/A | 0.079 |

1*Scores of the HEI-2005 were in quintiles and of the aMED were in 5 categories (0–2, 3, 4, 5–6, and 7–9). aMED, alternate Mediterranean Diet Score; HEI-2005, Healthy Eating Index-2005; N/A, not applicable.

2Estimated by using Cox proportional hazards regression models with the person-years as the underlying time metric after adjustment for age, race, smoking, alcohol intake, education, BMI, vigorous physical activity, usual activity, and total energy intake.

3HRs for head and neck cancer by categories of the HEI-2005 and aMED in the NIH-AARP Diet and Health Study.
We examined the association between each index and HNC risk by the stratum of smoking, alcohol consumption, and educational level (Figure 1). Risk estimates appeared similar across subgroups of alcohol intake and education (all P-interaction > 0.05). We observed a null association with each index in never smokers and an inverse association in former and current smokers in men, although these associations were not significantly different from each other (P-interaction > 0.24). For women, in contrast, we showed similar associations across smoking status, although associations did not reach statistical significance in never smokers (P-interaction > 0.13).

In an analysis of individual elements that compose the HEI-2005, only the component of total grains was associated inversely with HNC risk in both sexes. Whole fruit and calories from SoFAAS in HEI-2005 were significant in women but not men (see Table 1 under “Supplemental data” in the online issue). Results of the component analysis in the aMED also varied by sex. Whole grains, fruit, and red and processed meat were significant in women, whereas the component of legumes was significant in men (see Table 2 under “Supplemental data” in the online issue).

DISCUSSION

To our knowledge, this was the first prospective report to investigate the association between index-based dietary patterns and risk of incident HNC. We provided evidence for inverse associations between 2 dietary indexes and HNC risk, which suggested a beneficial effect when there was compliance with dietary guidance in the prevention of HNC.

A number of case-control and cross-sectional studies have explored the association between dietary patterns and risk of HNC overall or at subsites (18, 19, 27–36). Most studies identified dietary patterns by using a data-driven cluster or factor analysis (29–36). Other studies examined diet diversity, which measured the total number of different foods, and HNC (27, 28). Two studies have reported an inverse association between the traditional Mediterranean diet and cancers of the upper aerodigestive tract (18, 19), but only one study examined subsites of HNC (18). To our knowledge, no studies on other dietary indexes have been reported. Because previous studies on dietary patterns were retrospective or cross-sectional by design, these associations could have been affected by differential recall in case or control subjects or from systematic differences between case and control subjects.

The beneficial effect of a high score in dietary indexes may reflect synergistic effects of diverse food and numerous nutrients. For example, fruit and vegetables contain carotenoids and β-carotene, dietary fiber, and vitamin C, which might reduce HNC risk (9, 10, 37). The joint effect of components might be mediated by various biological pathways. The deregulation of the

**FIGURE 1.** Associations of the HEI-2005 and aMED with an incident head and neck cancer-subgroup analysis. HRs (95% CIs) indicate risk of developing head and neck cancer associated with per 10-score increase of the HEI-2005 and per 1-score increase of the aMED, which were estimated by using Cox proportional hazards regression models with person-years as the underlying time metric after adjustment for age, race, smoking (for subgroup analyses by alcohol intake and education; for subgroup analyses by smoking, we adjusted for the smoking dose), alcohol intake (for subgroup analyses by smoking and alcohol education), education (for subgroup analyses by smoking and alcohol intake), BMI, vigorous physical activity, usual activity throughout the day, and total energy intake. The P-int between subgroups of smoking, alcohol intake, and education and each index was tested by using likelihood ratio tests. HRs (95% CIs) in men and women overall are highlighted in bold and underlined text. aMED, alternate Mediterranean Diet Score; HEI-2005, Healthy Eating Index-2005; P-int, P-interaction.
Kelch-like ECH-associated protein 1/nuclear factor, erythroid 2-like 2 oxidative stress pathway has been frequently observed in HNC (38). Both the HEI-2005 and aMED are aligned with high intakes of fruit, vegetables, grains, nuts, and legumes, which are rich in antioxidants. The Mediterranean diet was shown to improve endothelial function by the reduced liberation of free radicals and less oxidative stress (11, 39), and a higher aMED score was associated with a lower oxidative stress (40). Inflammation is a major feature in carcinogenesis, and the overexpression of cyclooxygenase-2, Toll-like receptors, and galectins has been implicated in HNC (41). Higher diet-quality scores have been related to lower concentrations of inflammatory biomarkers, which may help circumvent HNC development (11, 42).

Healthier lifestyles related to the adherence to a healthy diet could partly explain the observed association, especially changes in smoking and alcohol-intake behaviors because these are 2 risk factors for HNC (3–6), and participants with high HEI-2005 or aMED scores tended not to smoke or drink heavily. As such, we adjusted for smoking and alcohol intake, which did not materially change the results. We performed stratified analyses by smoking and alcohol consumption. For never-drinking women, a significantly protective effect of each index was observed with the HR very close to the overall estimate. In men, stratification by alcohol revealed a stronger effect of each index in heavy alcohol users, but the majority of HNC cases in this group were identified in subjects with lower index scores; differences between the overall estimate and that in heavy drinkers could have been the result of chance. In addition, when we modified scores of the HEI-2005 and aMED by removing the alcohol component, we observed similar associations within strata of alcohol intake by using modified scores. Therefore, our results were unlikely to be greatly confounded by alcohol intake.

In stratified analyses by smoking, although we observed evidence of an inverse association in never smokers for women, associations in never-smoking men appeared to be null. It was not clear why associations may have differed between men and women, and differences across subgroups of smoking status and sex could have been due to chance. Residual confounding by smoking was possible in men, although smoking was a strong cause of HNC in both men and women in this trial and many other studies (3–5), and thus, it is unclear why residual confounding would have preferentially affected associations in men. Future studies with larger numbers of cases are needed to fully explore the possible differences between men and women. It would also be interesting to examine whether diets modify the carcinogenic processes of tobacco smoking, particularly in men.

In our study, we showed stronger inverse associations for each index in women. Explanations for these differences were unclear, although stronger associations with smoking and alcohol were previously observed in women in this cohort (5, 6). These differences in sex may feature other etiologic heterogeneities between men and women. A role of hormone-related factors has been postulated in HNC (43). However, associations in women were not affected by controlling for menopausal hormone therapy and age at menopause. Another possibility is HPV, the prevalence of which may have differed between men and women. HPV infection may drive HNC development in individuals without exposure to smoking and alcohol. The increase in oral and oropharyngeal cancers in recent years might be related to HPV infection (7, 44, 45). One recent study reported that 10-y risk of oropharyngeal cancer for HPV16 E6-seropositive never-smoker men were 3-fold that in E6-positive never-smoker women (46). It is likely that HNC risk can be attributed more to HPV infection in men than women.

A higher intake of total grains and fiber has been shown to reduce HNC risk in women in a previous report (37). We observed an inverse association of HNC with total grains in the HEI-2005 and aMED in women and total grains in the HEI-2005 in men. Recent case-control studies highlighted the importance of a dietary pattern rich in fruit and vegetables and low in processed meats for HNC prevention (31, 33). In our analyses, a high intake of whole fruit in the HEI-2005 and fruit in the aMED and low intake of red and processed meats in the aMED were inversely associated with HNC risk in women. Because we investigated multiple components, the significant association with some components could have been due to chance, which required additional studies to replicate. Furthermore, it is difficult to attribute the beneficial effect of a dietary index to any particular constituents because individual constituents are correlated with each other.

The strengths of this study were its prospective design, large sample size, and detailed information on potential confounders, which permitted a clear delineation of the temporal association between dietary patterns and the development of HNC. We also had limitations. First, an observational study cannot exclude the possibility of residual confounding by unmeasured or insufficiently controlled covariates. A healthy diet could be a surrogate for a favorable lifestyle. We lacked information on HPV infection. It remains a question whether HPV infection was the factor leading to the differential effect between men and women. The association between 2 indexes and cancer of the oral cavity in men was NS, for which the possible role of HPV infection requires investigation. Second, we likely had a misclassification in the dietary assessment because intake was assessed by self-report at a single time point. However, any differences in the diet would most likely have been nondifferential between cases and the cohort, which would have attenuated results toward the null. Third, our populations primarily consisted of non-Hispanic whites who were more educated than the general US population, such that the generalizability to other populations or ethnic groups was unclear. Fourth, index-based dietary patterns were derived on the basis of current knowledge and may not have captured the entire essence of a healthy diet.

In conclusion, the results from a large, well-established, long-term cohort study suggest an inverse association between higher scores in the HEI-2005 and aMED and HNC risk. The association appeared null in never-smoker men. Additional studies are merited to confirm our findings and further investigate underlying mechanisms. Our study suggests that following public health recommendations for a healthy diet may be associated with lower risk of HNC.

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