Prospective Studies of Body Mass Index with Head and Neck Cancer Incidence and Mortality

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SUMMARY

Background: Results of a pooled analysis of case-control studies show a higher risk of head and neck cancer (HNC) associated with a low body mass index (BMI) and a lower risk associated with being overweight or obese, compared to being normal weight. However, these results are prone to bias due to residual confounding by smoking, a strong risk factor, and possible weight loss prior to diagnosis. Using prospectively collected data from the Cancer Prevention Study-II cohort and the Nutrition cohort, we examined the association of BMI with HNC mortality and incidence, overall and by smoking status.

Methods: Mortality analyses included 1,383 cases among 1,059,153 participants; incidence analyses included 340 cases among 150,262 participants. Multivariable Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of BMI with HNC incidence and mortality.

Results: Overall, compared to the category of BMI 22.5-24.9 kg/m², the categories of BMI 25.0-29.9 kg/m² and ≥30.0 kg/m² were associated with a lower risk of HNC mortality but not incidence. In never smokers, there were no associations of BMI with HNC incidence or mortality. In smokers, BMI <22.5 kg/m² was associated with a higher risk of HNC mortality (HR=1.42, 95% CI 1.20, 1.67).

Conclusions: In this prospective cohort, there was no association between BMI and HNC incidence, although BMI was inversely associated with HNC mortality in smokers.

Impact: These suggest that there is no etiological relationship between BMI and HNC.
INTRODUCTION

Cancers of the oral cavity, pharynx, and larynx (referred to collectively as head and neck cancer (HNC) in our study) diagnosed in Europe and North America are due primarily to tobacco use and its synergistic actions with alcohol consumption (1, 2). However, approximately 75% of HNC is attributed to tobacco and alcohol (of which only 4% is due to alcohol alone) (2), suggesting that other factors may be associated with risk of these cancers. For example, results of several individual case-control studies suggest obesity may be a risk factor for HNC (3-11). However, in those studies (3-11), power was limited to assess the associations in never smokers, and, therefore, residual confounding could not be ruled out. In a large, pooled analysis of 17 international case-control studies of HNC (12,716 cases and 17,438 controls), low body mass index (BMI <18.5 kg/m²) was associated with a higher risk of HNC compared to subjects with a normal BMI (18.5-24.9 kg/m²), while BMI ≥25.0 kg/m² was associated with a lower risk (12). In stratified analyses, the elevated risk of HNC associated with a low BMI persisted for both smokers/drinkers and never smokers/never drinkers, whereas, the reduced risk related to higher BMI was limited only to smokers/drinkers suggesting the possibility of residual confounding by smoking and drinking for the low BMI results. Another concern is that retrospective studies might be prone to misclassification of BMI of cases due to weight loss before diagnosis of HNC (12). Therefore, large studies of HNC with prospectively collected weight, smoking, and drinking data are needed to rule out these concerns. The American Cancer Society (ACS) Cancer Prevention Study-II (CPS-II), a large prospective study with long follow-up and detailed information on body size, lifetime smoking history, and alcohol consumption, provides an opportunity to assess the associations of body size with HNC incidence and mortality overall and by smoking status.
MATERIALS AND METHODS

Mortality Analyses. Individuals in the mortality analysis were drawn from the approximately 1.2 million participants in CPS-II cohort, a nationwide prospective mortality study initiated in 1982 and described in detail elsewhere (13, 14). Briefly, 521,555 men and 685,748 women 30 years of age or older were enrolled by ACS volunteers in all 50 states, the District of Columbia, and Puerto Rico. At entry, participants completed confidential mailed questionnaires on demographic information, weight, height, lifetime tobacco use, alcohol consumption, and other lifestyle factors. Exposure data used in the mortality analyses were based on the information collected at enrollment in 1982.

The primary endpoint for the mortality analyses was death from HNC (based on International Classification of Disease for Oncology for the oral cavity, oropharynx, hypopharynx, and larynx as previously defined (15)) between the time of enrollment and December 31, 2008. Vital status of participants in the mortality cohort was determined through personal inquiries by volunteers in September of 1984, 1986, and 1988, with vital status validated and cause of death determined by death certificate. After 1988, vital status and cause of death were ascertained through biennial linkage to the National Death Index for 99.4% of participants known to have died (16).

In the mortality analysis, individuals were excluded if they reported a history of cancer at baseline (except non-melanoma skin cancer) (n=82,326), had missing data for height or weight on their respective enrollment questionnaires (n=25,021), had BMI values in the upper and lower 0.1% (n=2,154), or died of lip cancer (n=3). After exclusions, 1,074,914 participants remained in the analytical cohort.
**Incidence Analyses.** In 1992-3, a subgroup of 184,188 CPS-II participants (17), who resided in 21 states with population-based state cancer registries and were 50-74 years of age were enrolled in the CPS-II Nutrition Cohort. At baseline, the participants completed a mailed questionnaire on demographic, medical, behavioral, environmental, and occupational factors, including weight, height, lifetime tobacco, and alcohol consumption. Follow-up questionnaires were sent to cohort members every two years starting in 1997 to update exposure information and to ascertain newly diagnosed cancer outcomes. Exposure data used in the incidence analyses were based on the information collected at enrollment in 1992.

In the incidence analysis, individuals were excluded if they did not return any survey and were alive as of December 31, 1997 (n=6,276), reported a history of cancer at baseline (except non-melanoma skin cancer) (n=22,860), had missing data for height or weight on their respective enrollment questionnaires (n=2,306), or BMI values in the upper and lower 0.1% (n=306). Self-reported HNC were verified with medical record (63.2% of all HNCs) or state tumor registries (34.0%); fatal cases were identified through linkage with the National Death Index (2.8%). We excluded 14 participants whose self-reported HNC cancer could not be verified. Remaining for incidence analysis were 152,426 participants.

**Exposure Definition.** Height and weight was self-reported on the 1982 baseline survey, and weight was reported again on the 1992 baseline surveys for the mortality and incidence analyses, respectively. BMI was computed as weight (kg) divided by height squared (m²) and then categorized as <22.5, 22.5-24.9, 25.0-29.9, ≥30.0 kg/m². The bounds for the lower category deviated from the World Health Organization cut-points (18) to be consistent with pooled analyses of BMI and mortality (19, 20) that indicate individuals with a BMI 22.5 to 24.9 kg/m²
have the lowest mortality. Data on education was ascertained on the 1982 survey; alcohol intake and smoking were also based on responses to the 1982 and 1992 baseline surveys.

Statistical Analyses. Participants contributed person-time to the mortality analysis for the interval that started two years after the completion of their 1982 survey until they died, were lost to follow-up as of September 1, 1988 because of insufficient information for record linkage, or reached the end of the follow-up period (December 31, 2008). For the incidence analysis, participants contributed person-time to the analysis for the interval that started two years after the completion of their 1992 survey until they were censored at the date of diagnosis for those diagnosed with head and neck cancer or other cancers, date of death for those who died before the end of follow-up, date of last survey returned for those lost to follow-up before the end of follow-up, or June 30, 2007 for those that reached the end of the follow-up period.

Multivariable-adjusted Cox proportional hazard regression models (21) were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the associations of BMI with HNC incidence and mortality. All Cox models were stratified on single year of age at enrollment. HRs for the mortality analysis were adjusted for sex, race, education, alcohol intake in 1982, and joint smoking variable of status in 1982, years since last cigarette, and cigarettes per day. HRs for the incidence analysis were adjusted for sex, education, alcohol intake in 1992, and cigarette smoking status in 1992. The Cox proportional hazards assumption was evaluated by testing for an interaction by time in the model. The assumption was violated for both the mortality analysis (p=0.023) and the incidence analysis (p=0.018) if follow-up time started at the date of the enrollment questionnaire; however, the assumption for the mortality analysis (p=0.088) and the incidence analysis (p=0.46) was satisfied after exclusion of the first two years
of follow-up, which included 15,761 censoring events (50 HNC deaths) in the mortality analysis and 2,164 censoring events (51 HNC cases) in the incidence analysis.

Reported p-values are two-sided and were considered statistically significant if <0.05. p-values for linear trend were calculated based on the median values of BMI within each BMI category treated as an ordinal variable.

Associations of BMI with HNC incidence and mortality also were examined separately in never smokers and ever smokers. Ever cigar or pipe only smokers were excluded from stratified analyses because they comprised a small subgroup. We stratified analyses by whether the tumor was located in the non-oropharynx region (defined as the oral cavity, hypopharynx, and larynx) or the oropharynx region. Stratification by location was used as a crude proxy for HPV status of the tumors, since the oropharynx is the HNC region proposed to have a strong HPV etiology (22). Cases who died prior to 1992 were excluded from the stratified analyses in the mortality cohort, because we could not distinguish the location of the tumor from the death certificate.

All analyses were performed in Statistical Analysis Software (SAS, version 9.2).

RESULTS

In the CPS-II mortality cohort, obese participants were less likely to be college educated, an alcohol drinker, or a current smoker (Table 1); differences in covariates by BMI were similar, but less pronounced in the CPS-II Nutrition Cohort (data not shown). In the CPS-II mortality cohort, 1,383 HNC deaths occurred during follow-up; and, in the CPS-II Nutrition cohort, there were 340 HNC cases diagnosed during follow-up.

In the incidence analysis, BMI was not associated with HNC overall or by smoking status (Table 2).
Overall, lean individuals (BMI <22.5 kg/m²) had a 28% higher risk of dying of HNC (Table 2), while overweight (BMI 25.0-29.9 kg/m²) or obese (BMI ≥30.0 kg/m²) individuals had a lower risk of HNC mortality, compared to normal weight (BMI 22.1-24.9 kg/m²) individuals in the multivariable-adjusted model. This pattern of association was observed among ever smokers but not among the never smokers. For never smokers, BMI was not associated with HNC mortality. Among all CPS-II participants, relative risk of oropharynx cancer mortality was not associated with BMI; however, lean individuals had a higher risk of non-oropharynx cancer, and overweight and obese individuals had a lower risk of non-oropharynx cancer (Table 3).

**DISCUSSION**

In this prospective cohort study of BMI and HNC, there were no associations between BMI and risk of HNC incidence overall, by smoking status, or by tumor site. The lower risk of HNC mortality associated with overweight and obesity was limited to smokers, and there was evidence of an elevated risk of HNC mortality for lean smokers. BMI was not associated with HNC mortality in never smokers.

The relationship between BMI and HNC incidence has not been examined previously in prospective studies. A pooled analysis of case-control studies reported a 50% lower risk for overweight and obesity and a twofold higher risk for leanness in overall analyses and those limited to ever smokers; the association between HNC risk and leanness persisted even in non-smokers (12). These results differ from the lack of association between BMI and HNC incidence observed in this prospective study. One possible reason for the different results between these studies is that the cases’ recall of their usual weight in retrospective studies might be influenced
by weight loss prior to diagnosis causing a downward shift of BMI categories for some cases. The differential misclassification could cause spurious positive associations for the low BMI category and inverse associations for the overweight and obesity categories as observed in the pooled analysis of case-control studies with retrospective collection of weight (12).

The null associations of BMI with HNC mortality for never smokers but not for ever smokers suggests that factors involved in progression and prognosis may differ for smoking-related tumors compared to non-smoking related tumors. Evidence in favor of this argument is supported by the observed inverse association with BMI for risk of non-oropharyngeal cancer death, which has a poor prognosis (23), but not for death of oropharyngeal cancer, which has a more favorable prognosis (23, 24). However, survival analyses of HNC outcomes are needed to evaluate a possible relationship with BMI.

BMI and HNC mortality have been examined in a pooled analysis of prospective data from 57 cohort studies (20). However, direct comparisons with results should be made cautiously as the outcome was defined as death from cancers of the upper aerodigestive tract, including deaths from cancers of the mouth, pharynx, larynx, and esophagus. A statistically significant lower risk of death from cancers of the upper aerodigestive tract was observed in lifelong never smokers with higher BMI levels ranging from 15-25 kg/m² (54 HNC deaths; HR=0.35, 95% CI 0.16-0.74 per 5 kg/m²) and no association was observed for individuals with a higher BMI levels ranging from 25-50 kg/m² (60 HNC deaths; HR=1.00, 95% CI 0.56-1.78 per 5 kg/m²). Reasons for the strong inverse association for BMI values ranging from 15-25 kg/m² in that pooled analysis are unknown but may be due to chance, the heterogeneous outcome definition, small number of outcomes, the limited adjustment for confounding, or a relationship of BMI with HNC survival among non-smokers. Furthermore, while those results suggest that
residual smoking does not confound the relationship between low BMI and HNC mortality, it does not address a relationship between BMI and HNC incidence.

The major strengths of this study are the prospective design, long follow-up time, and examination of mortality and incidence. In particular, the ability to examine weight many years prior to detectable disease allowed us to avoid the influence of weight loss secondary to disease. However, we did not update BMI or smoking status. If some smokers quit in the follow-up time, their person-time could be misclassified for smoking status and for BMI if the former smoker experienced weight gain after quitting smoking. If there is a true inverse association between BMI and head and neck cancer incidence, misclassification of BMI due to weight gain secondary to quitting would attenuate associations toward the null. However, given that the incidence results were nearly equivalent for never smokers and ever smokers, this bias is unlikely to have had a significant influence on the observed results.

Our incidence analyses are based on a relatively small number of cases, although we still had greater than 80% power to detect associations larger than 1.5 (or less than 0.7) in the extreme categories of BMI. Moreover, we had adequate power to exclude the possibility that the relationship between BMI and HNC incidence was as extreme as suggested by the pooled case-control analysis (12). We did not have tumor tissues to determine the presence of HPV, although examining HRs for HPV-associated oropharyngeal cancers (22) separately from smoking-associated non-oropharyngeal cancers did not reveal any meaningful differences in associations of incidence with BMI. Furthermore, study participants were predominantly of European ancestry and in higher SES strata. While these factors may affect the generalizability of the confounding effects of smoking on the BMI-HNC association, it is unlikely that SES and race affect the underlying conclusion that BMI is not causally related to HNC etiology.
While we were able to examine BMI-HNC associations stratified by smoking status, power was limited to further stratify by alcohol intake. It is important to also consider the potential confounding effects of alcohol intake on the association between BMI and risk of HNC because it is well established that alcohol drinkers, particularly moderate to heavy drinkers as shown in our study, tend to have a lower BMI and a higher risk of HNC (particularly among smokers) (2, 22). Additionally, stratified analyses of the association between BMI and non-oropharyngeal HNC risk among never smokers and never drinkers would further support the lack of a causal role of BMI in HNC etiology. A large pooled analysis is necessary to provide more detailed assessment of the relationship of BMI with HNC in never smokers and never drinkers.

**FUNDING**

This work was supported by the intramural research program at the American Cancer Society (Atlanta, GA).
Table 1. Age-adjusted frequencies of selected baseline characteristics reported in 1982 by categories of body mass index (BMI) in the Cancer Prevention Study (CPS)-II Cohort, 1982-2008

<table>
<thead>
<tr>
<th>Categories of BMI (kg/m²)</th>
<th>&lt;22.5</th>
<th>22.5-24.9</th>
<th>25.0-29.9</th>
<th>≥30.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=272,128 (25.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=279,689 (26.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=391,117 (36.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=116,219 (11.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median BMI (IQR)</td>
<td>21.0 (20.0-21.8)</td>
<td>23.7 (23.1-24.4)</td>
<td>26.6 (25.8-28.1)</td>
<td>32.1 (30.9-34.4)</td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>55 (48-63)</td>
<td>57 (50-64)</td>
<td>57 (50-64)</td>
<td>55 (49-62)</td>
</tr>
</tbody>
</table>

Sex
- Men: 57,996 (21.8) 124,649 (44.4) 230,889 (58.7) 48,187 (41.0)
- Women: 214,132 (78.2) 155,040 (55.6) 160,228 (41.3) 68,032 (59.0)

Race
- White: 258,008 (95.0) 263,835 (94.3) 363,813 (92.9) 103,035 (88.7)
- Non-white/ missing: 14,120 (5.0) 15,854 (5.7) 27,304 (7.1) 13,184 (11.3)

Education
- College graduate or more: 87,023 (31.5) 89,983 (32.4) 116,005 (29.9) 26,281 (22.2)
- Some college: 82,912 (30.5) 79,695 (28.6) 108,715 (27.9) 31,821 (27.0)
- High school graduate: 69,853 (26.0) 70,935 (25.4) 99,300 (25.3) 32,608 (27.7)
- Less than high school graduate: 28,546 (10.7) 35,100 (12.2) 61,284 (15.5) 23,476 (21.3)
- Missing: 3,794 (1.4) 3,976 (1.4) 5,813 (1.5) 2,033 (1.8)

Alcohol
- Non-drinker: 144,812 (53.1) 146,107 (52.1) 208,980 (53.5) 74,933 (65.0)
- Former drinker: 4,400 (1.6) 4,629 (1.7) 6,737 (1.7) 2,132 (1.8)
- <1 drink/day: 57,514 (21.0) 59,213 (21.3) 79,132 (20.3) 19,847 (16.8)
- 1 drink/day: 22,340 (8.3) 22,524 (8.1) 27,434 (7.0) 4,988 (4.3)
- 2-3 drinks/day: 27,501 (10.2) 29,203 (10.5) 40,134 (10.2) 7,719 (6.6)
- 4+ drinks/day: 13,851 (5.2) 16,301 (5.9) 26,290 (6.7) 5,901 (5.0)
- Missing/unknown: 1,710 (0.6) 1,712 (0.6) 2,414 (0.6) 699 (0.6)

Smoking
- Never: 117,226 (42.7) 114,451 (40.9) 148,605 (38.2) 51,938 (45.1)
- Current: 70,839 (26.1) 57,404 (21.3) 70,140 (18.2) 18,124 (15.1)
- Former: 58,630 (21.6) 67,948 (24.3) 102,676 (26.0) 28,153 (24.0)
- Ever/unknown status: 4,863 (1.8) 4,589 (1.6) 6,292 (1.6) 2,104 (1.8)
- Pipe/cigar: 10,204 (3.9) 24,627 (8.7) 47,501 (12.0) 10,082 (8.6)
- Missing: 10,366 (3.8) 10,670 (3.7) 15,903 (4.1) 5,818 (5.2)
Table 2. Multivariate-adjusted\(^1\) hazard ratios (HR) and 95% confidence intervals (CI) of the associations between head and neck cancer incidence and body mass index\(^2\) among men and women in the Cancer Prevention Study (CPS)-II Nutrition Cohort, 1992-2007

<table>
<thead>
<tr>
<th>Categories of Body Mass Index (kg/m(^2))</th>
<th>Entire cohort</th>
<th>Never smokers</th>
<th>Ever smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22.5</td>
<td>58/352,483</td>
<td>14/176,790</td>
<td>44/172,290</td>
</tr>
<tr>
<td>22.5-24.9</td>
<td>85/447,269</td>
<td>19/206,623</td>
<td>65/236,515</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>150/709,021</td>
<td>37/303,153</td>
<td>113/400,622</td>
</tr>
<tr>
<td>≥30.0</td>
<td>47/262,386</td>
<td>8/119,468</td>
<td>39/140,273</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.05 (0.75, 1.47)</td>
<td>0.97 (0.49, 1.96)</td>
<td>1.21 (0.82, 1.79)</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>1.02 (0.78, 1.34)</td>
<td>1.32 (0.76, 2.30)</td>
<td>0.91 (0.67, 1.23)</td>
</tr>
<tr>
<td></td>
<td>1.06 (0.74, 1.52)</td>
<td>0.89 (0.39, 2.06)</td>
<td>1.00 (0.67, 1.49)</td>
</tr>
<tr>
<td>P-values for linear trend(^3)</td>
<td></td>
<td></td>
<td>0.84</td>
</tr>
</tbody>
</table>

- HRs were adjusted for sex (men, women), education (college graduate or more, some college, high school graduate, less than a high school education, missing), alcohol intake at baseline (non-drinker, <1 drink/day, 1 drink/day, 2+ drinks/day, missing or unknown), and cigarette smoking status at baseline (non-smoker, current smoker, former smoker, ever smoker/unclassifiable, and missing). All Cox models were stratified on single year of age at enrollment.
- Body mass index (BMI, kg/m\(^2\)) was calculated using weight in kilograms divided by height in meters squared.
- P-values for linear trend were calculated based on the median values of the body mass index categories treated as an ordinal variable.
- Non-oropharynx cancer category was comprised of cancers diagnosed in the oral cavity, hypopharynx, and larynx.
Table 3. Multivariate-adjusted\(^1\) hazard ratios (HR) and 95% confidence intervals (CI) of associations between head and neck cancer mortality and body mass index\(^2\) among men and women in the Cancer Prevention Study (CPS)-II Cohort, 1982-2008

<table>
<thead>
<tr>
<th>Categories of Body Mass Index (kg/m(^2))</th>
<th>Entire cohort</th>
<th>P-values for linear trend(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;22.5</td>
<td>22.5-24.9</td>
</tr>
<tr>
<td>No. deaths/ person-time</td>
<td>396/5,990,328</td>
<td>404/6,097,080</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.28 (1.11, 1.47)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

| Never smokers                           | No. deaths/ person-time | 37/2,679,551 | 47/2,592,368 | 68/3,303,824 | 21/1,133,505 |
|                                          | HR (95% CI)              | 0.90 (0.58, 1.39) | 1.00 | 1.07 (0.74, 1.56) | 1.15 (0.68, 1.93) | 0.33 |

| Ever smokers                            | No. deaths/ person-time | 301/2,908,564 | 284/2,779,955 | 297/3,766,528 | 69/1,008,076 |
|                                          | HR (95% CI)              | 1.42 (1.20, 1.67) | 1.00 | 0.65 (0.55, 0.76) | 0.68 (0.53, 0.89) | 2.4x10\(^{-15}\) |

| Oropharynx cancer in entire cohort       | No. deaths/ person-time | 53/ 5,990,328 | 48/ 6,097,080 | 65/ 8,390,988 | 17/ 2,463,577 |
|                                          | HR (95% CI)              | 1.35 (0.91, 2.02) | 1.00 | 0.89 (0.61, 1.30) | 1.00 (0.57, 1.74) | 0.14 |

| Non-oropharynx cancer in entire cohort   | No. deaths/ person-time | 325/ 5,990,328 | 336/ 6,097,080 | 390/ 8,390,988 | 85/ 2,463,577 |
|                                          | HR (95% CI)              | 1.28 (1.10, 1.50) | 1.00 | 0.75 (0.64, 0.86) | 0.74 (0.59, 0.95) | 5.1x10\(^{-10}\) |

\(^1\)HRs were adjusted for sex (men, women), race (white, non-white/missing), education (college graduate or more, some college, high school graduate, less than a high school education, missing), alcohol intake at baseline (non-drinker, former drinker, <1 drink/day, 1 drink/day, 2-3 drinks/day, 4+ drinks/day, missing or unknown), and joint smoking variable of status at baseline, years since last cigarette, and cigarettes per day (non-smoker, quit 20+ years, 10-19 years since last quit and smoked ≤20 cigarettes per day, 10-19 years since last quit and smoked >20 cigarettes per day, 2-9 years since last quit and smoked ≤20 cigarettes per day, 2-9 years since last quit and smoked >20 cigarettes per day, <2 years since last quit and smoked ≤20 cigarettes per day, <2 years since last quit and smoked >20 cigarettes per day, current smoker who smokes ≤10 cigarettes per day, current smoker who smokes 11-20 cigarettes per day, current smoker who smokes 21-30 cigarettes per day, current smoker who smokes 31-40 cigarettes per day, current smoker who smokes 41+ cigarettes per day, and unclassifiable/unknown status). All Cox models were stratified on single year of age at enrollment.

\(^2\)Body mass index (BMI, kg/m\(^2\)) was calculated using weight in kilograms divided by height in meters squared.

\(^3\)P-values for linear trend were calculated based on the median values of the body mass index categories treated as an ordinal variable.

\(^4\)Non-oropharynx cancer category was comprised of cancers diagnosed in the oral cavity, hypopharynx, and larynx.
References
