Interaction between known risk factors for head and neck cancer and socioeconomic status: the Carolina Head and Neck Cancer Study

Gaelen Stanford-Moore¹,², Patrick T. Bradshaw³, Mark C. Weissler⁴, Jose P. Zevallos⁵, Paul Brennan⁶, Devasena Anantharaman⁶, Behnoush Abedi-Ardekani⁶, Andrew F. Olshan⁷

Received: 23 December 2017 / Accepted: 24 July 2018 / Published online: 1 August 2018
© The Author(s) 2018

Abstract

Prior studies of squamous cell carcinoma of the head and neck (SCCHN) have explored the effect of socioeconomic status (SES) as an independent risk factor; however, none have investigated the interaction of known risk factors with SES. We examined this using the North Carolina Head and Neck Cancer Epidemiology Study, a population-based case–control study. Incident cases of SCCHN from North Carolina between 2002 and 2006 (n = 1,153) were identified and age, sex, and race-matched controls (n = 1,267) were selected from driver license records. SES measures included household income, educational attainment, and health insurance. Logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI). Current smoking was more strongly associated with SCCHN among those households making < $20,000/year [OR 5.11 (3.61–6.61)] compared to household incomes > $50,000/year [OR 2.47 (1.69–3.25); p interaction < 0.001]. Current drinking was more strongly associated with SCCHN in household incomes < $20,000 [OR 2.91 (2.05–3.78)] compared to > $50,000/year [1.28 (0.97–1.58); p interaction < 0.001]. Current drinkers with less than high school education or income < $20,000 had nearly threefold odds of never-drinkers in the same SES category [OR 2.91 (2.05–3.78); 2.09 (1.39–2.78), respectively]. Our results suggest that the relationship of smoking and alcohol use may be stronger among those of lower SES.

Keywords Case–control studies · Epidemiology · Head and neck cancer · Risk factors · Socioeconomic status · Tobacco · Alcohol

Introduction

Tobacco and alcohol use have been shown to be consistent risk factors for head and neck cancer [1–4]. However, as the prevalence of smoking decreases in the United States [5], new risk factors have emerged including human papillomavirus [6], poor oral health [7, 8], and genetic factors [9]. Similarly, low socioeconomic status (SES) has been strongly associated with development of oral cancer in men [10]. A 2015 study using pooled international data from over 23,000 cases examined the effects of income and education on head and neck cancer occurrence. They found that fewer years of education and lower income were associated with an increase in disease development. This risk was attenuated when adjusting for alcohol and tobacco use [11]. Here, as with other studies [12–14], socioeconomic status was examined as an independent risk factor, or adjusted as a confounder. However, it is unclear whether the association of risk factors, such as tobacco and alcohol, is modified...
by SES. A comprehensive description of the interaction between risk factors and SES may offer new insights into the nature of the interaction and clarify other unrelated effects of SES.

It is possible that individuals with lower SES may be more susceptible to the effects of tobacco, alcohol, and other risk factors. To our knowledge, no study to date has explored the joint effect of socioeconomic status and other known risk factors on squamous cell carcinoma of the head and neck (SCCHN). We examined the potential for interaction between various known risk factors for SCCHN and SES in a large population-based study in a racially diverse population.

Materials and methods

This study uses data previously collected by the Carolina Head and Neck Cancer Epidemiology Study (CHANCE) [15]. Briefly, CHANCE is a population-based case–control study of patients with newly diagnosed first primary invasive SCCHN between 1 January 2002 and 28 February 2006 in North Carolina, United States.

Cases were 20–80 years of age at the time of diagnosis, residents of a 46-county region in North Carolina, and had never been previously diagnosed with head and neck cancer. Controls were identified through the North Carolina Department of Motor Vehicle driver license records and were frequency matched by age, race, and sex. Contact and cooperation rates were 98 and 82% for cases, and 80 and 61% for controls, respectively. Demographic, lifestyle, oral health, dietary, and other risk factor information was collected using a structured questionnaire during an in-home visit. The study was approved by the Institutional Review Board (IRB) of the University of North Carolina at Chapel Hill, and all participating institutions.

The CHANCE questionnaire was completed by 1,389 eligible cases and 1,396 eligible controls. We excluded 21 cases of lip cancer (1.5% of all cases), 28 cases and 18 controls who specified ‘other race’ (46 or 1.7%), and 68 participants (51 cases and 17 controls) who used a proxy during interview. An additional 136, or 10.6%, of eligible cases and 94, or 6.7%, of eligible controls were excluded for missing covariate information. The final study population in our complete case analysis included 1,153 cases and 1,267 controls.

For the assessment of HPV tumor status, patients who had lip and hypopharynx cancers, those for whom the hospital would not release tumor blocks, and those who had completed only proxy interviews were excluded from p16 tumor immunohistochemistry. All patients with oropharyngeal cancers (N = 248) and a random sample of patients with non- oropharyngeal cancers (N = 244) (because the relevance of HPV in non-oropharyngeal cancer has not been established [16]) were selected for the evaluation of p16-positivity [17].

Exposure and covariate definitions

Primary exposures of interest included tobacco use, alcohol intake, oral health status, and measures of SES. Cases were asked about exposures the year prior to diagnosis while controls were asked about current use. Tobacco use was defined as (1) never- [ref], ex-, or current smokers; (2) number of cigarettes per day (never-smoker [ref], 0–19, 20–39, 40+); (3) number of years smoked (4) pack-years smoking (never- [ref], 1–10, 11–19, 20–39, 40–49, 50+) (4) never- [ref]/ever-use of smokeless tobacco. Alcohol use was defined as (1) never- [ref], ex-, or current drinker and (2) number of years consuming beer, wine, or liquor (3) quintiles of cumulative lifetime alcohol consumption [grams (g) of ethanol from beer, liquor, and wine; never-drinker [ref], 1–11,232 g, 11,232–204,496 g, 204,496–927,946 g, and ≥ 927,946 g].

In the United States, a standard alcoholic drink is defined as containing 14 g of alcohol [18], therefore the highest quintile of cumulative alcohol consumption is equivalent to more than 25 drinks per week for 50 years. Self-reported oral health variables, selected based on a previous CHANCE study [15], included (1) history of self-reported tooth mobility, or “teeth loose in their socket due to disease” (yes [ref]/no) and (2) one or more routine (non-emergency) dental visits during the decade prior to SCCHN diagnosis (yes [ref]/no). SES factors included (1) household income (> $50,000 per year [ref], $20,000–$50,000 per year, and < $20,000 per year); (2) education (some college or more [ref], high school graduation or 12 years of education but no further, 11 years or fewer of education), and (3) insurance type [none [ref], private, Medicare/Medicaid, other (including Veterans’ Affairs (VA)/military healthcare, TRICARE/CHAMPUS/CHAMPVA, and “other” indicated on the questionnaire)]. Other factors, which served as potential confounders, included environmental tobacco smoke and family history of cancer. Environmental tobacco was defined as never [ref]/ever being exposed to tobacco smoke in the workplace or home. Family history of cancer was defined as having any first-degree relative with family history of any cancer (yes [ref]/no).

Statistical analysis

We calculated odds ratios (OR) and 95% confidence intervals (CI) for each exposure and SCCHN risk using unconditional logistic regression. We evaluated multiplicative interaction of tobacco use, alcohol use, and oral health status by SES with an exposure-SES product term. Likelihood ratio tests (LRT) were conducted to compare the models with the multiplicative term to the same model without it. Given low
statistical power for interaction analysis, an a priori alpha of 0.10 was used as the significance threshold. All analyses were conducted in Stata v14.2. The primary analyses included the modification of tobacco and alcohol use (never, ex-, current), and oral health status associations by SES, but we also conducted additional analyses on the interaction between cigarette duration of use, smokeless tobacco use, quantity of alcohol use, and oral health risk factors and SES.

Minimally adjusted models included only the joint primary exposures (tobacco or alcohol use or oral health and SES) and the matching factors [age (continuous), race (white, African American), sex (male, female)]. Potential confounders were identified using a directed acyclic graph approach [19]. The fully adjusted model included the matching factors [age (continuous), race (white, African American), sex (male, female)] plus additional covariates: oral health parameters, smokeless tobacco, family history of cancer, and SES factors.

Given the known association between HPV infection and SCCHN, particularly oropharyngeal cancer, initial analyses were repeated, stratifying by HPV positivity. p16 status had only been tested in patients who had oropharyngeal cancers \( n = 248 \) and a random sample of patients who had non-oropharyngeal cancers \( n = 244 \). p16 was chosen as the marker for HPV based on a previous CHANCE study that determined using p16, rather than both HPV DNA PCR and p16 expression, did not change point estimates [8]. HPV-positive tumors were compared to controls and, separately, HPV-negative tumors were compared to controls, assessing of odds of SCCHN within each stratum of SES. The effect of SES was investigated after stratification by tumor site. Cases within each tumor site were compared to all controls.

A sensitivity analysis was undertaken to compare the results of the primary analysis with reclassification of insurance category. The primary main effect and interaction models with the insurance category were compared to the same models with a re-categorization of insurance. Medicaid and Medicare insurance types were subdivided, to determine the specific effects and interactions related to the two insurance types separately.

**Results**

Among cases, 76.3% were male and 74.4% identified as white. Among controls, 69.4% were male and 80.8% identified as white (Table 1). At the time of the interview, cases were slightly younger than controls [mean (median) age of cases: 58.9 (59) years, controls: 61.5 (63)]. The distribution of the primary cancer site for cases (of 1,153) was 163, (14%) oral, 317 (27%) oropharyngeal (OPC), 52 (5%) hypopharyngeal, 416 (36%) laryngeal, and 205 (18%) not otherwise specified. Of all cases who had tumors tested for p16 as a marker of HPV infection, 44% (192 of 434) were p16-positive. A total of 144 (of 248, 58%) of OPC cases were p16 positive. Of non-oropharyngeal cases, 19 (20%) of laryngeal cases, 14 (22%) of oral cavity cases, and 15 (26%) of NOS cases were p16 positive.

**Main effects of tobacco, alcohol, and oral health variables**

Table 2 presents the description of known risk factors for SCCHN development, fully adjusted for the matching factors of age, race, and sex, plus pack-years smoking history, lifetime alcohol consumption, smokeless tobacco use, family history of cancer, and oral health parameters (except the exposure of interest). Current smokers were four times more likely to develop SCCHN compared to never-smokers [OR 4.16 (3.21–5.39)]. Longer duration of cigarette smoking and greater number of cigarettes smoked daily were strongly associated with increased odds of SCCHN [OR smoking 50 or more years: 5.83 (3.97–8.57); OR 50 or more cigarettes daily: 3.80 (2.28–6.32)] compared to never-smokers. Lifetime total alcohol consumption was positively associated with odds of SCCHN, with almost four times greater odds of SCCHN in individuals with the highest lifetime consumption of alcohol compared to never-drinkers [OR 3.69 (2.59–5.24)]. Oral health factors, including self-reported history of a loose permanent tooth and lack of routine dental visit within the decade preceding SCCHN diagnosis were both associated with increased odds of SCCHN, respectively [OR 1.48 (1.20–1.83) and OR 1.84 (1.45–2.31)].

**Main effects of SES variables**

Marked differences in income were noted between cases and controls (Table 3). Years of education were inversely associated with odds of SCCHN, with participants who attained less than a high school education having nearly four times the odds of SCCHN, compared to those who completed some college or more (Table 3, OR 3.97 (3.18–4.96)). Adjustment for tobacco use, alcohol use, and oral health factors, which could be potential mediators, further attenuated the contribution of SES to odds of SCCHN. The odds were higher with minimal adjustment (only matching factors, OR 3.97 (3.18–4.96)) versus adjustment for matching factors, plus family history of cancer, and other SES variables [OR 1.81 (1.35–2.42)].

Stratified by tumor site, there was a general trend of increasing odds of SCCHN with lower income and fewer years of education. For example, SCC of the oral cavity had the strongest association with low income and less education [OR 2.24 (1.21–4.14); OR 1.43 (0.86–2.39) for income < $20,000 and less than high school education, respectively] (Supplemental Table 1).
Interaction between tobacco use and SES

Table 4 shows the interaction results between ever-smoking cigarettes and SES variables. Compared to never-smokers with an annual income greater than $50,000, individuals who were current smokers and had an income less than $20,000 had more than five times the odds of SCCHN [OR 5.11 (3.61–6.61)], while current smokers who had incomes
### Table 2: Relationship of known risk factors and odds of SCCHN in CHANCE, 2002–2004

| Factor                              | Cases (n=1,289) | Controls (n=1,361) | Minimally adjusted OR<sup>a</sup> (95% CI) | Fully adjusted OR<sup>b</sup> (95% CI) |
|-------------------------------------|----------------|-------------------|------------------------------------------|----------------------------------|
| **Smoking status**                  |                |                   |                                          |                                  |
| Never-smoker                        | 170 (13.19)    | 521 (38.28)       | Ref                                      | Ref                              |
| Ex-smoker                           | 382 (29.64)    | 572 (42.03)       | 2.09 (1.67–2.63)                         | 1.51 (1.17–1.95)                  |
| Current smoker                      | 737 (57.18)    | 268 (19.69)       | 7.84 (6.20–9.91)                         | 4.16 (3.21–5.39)                  |
| **Years smoked**                    |                |                   |                                          |                                  |
| Never-smoker                        | 170 (13.19)    | 521 (38.28)       | Ref                                      | Ref                              |
| 1–19                                | 116 (9.00)     | 290 (21.31)       | 1.12 (0.83–1.51)                         | 1.02 (0.75–1.39)                  |
| 20–39                               | 491 (38.09)    | 328 (24.10)       | 4.21 (3.31–5.36)                         | 2.64 (2.03)                      |
| 40–49                               | 330 (25.60)    | 142 (10.43)       | 8.76 (6.57–11.69)                        | 4.55 (3.32–6.22)                  |
| 50 or more                          | 182 (14.12)    | 80 (5.88)         | 11.08 (7.34–15.85)                       | 5.83 (3.97–8.57)                  |
| **Number of cigarettes per day**    |                |                   |                                          |                                  |
| Never-smoker                        | 170 (13.19)    | 521 (38.28)       | Ref                                      | Ref                              |
| 1–19                                | 225 (17.46)    | 332 (24.39)       | 1.94 (1.49–2.52)                         | 1.49 (1.13–1.98)                  |
| 20–39                               | 580 (45.00)    | 380 (27.92)       | 4.79 (3.80–6.04)                         | 2.85 (2.20–3.67)                  |
| 40–49                               | 228 (17.69)    | 97 (7.13)         | 7.70 (6.64–10.50)                        | 3.82 (2.71–5.37)                  |
| 50 or more                          | 86 (6.67)      | 31 (2.28)         | 8.53 (5.30–13.73)                        | 3.80 (2.28–6.32)                  |
| **Pack-years smoking history**      |                |                   |                                          |                                  |
| Never-smoker                        | 170 (13.19)    | 521 (38.28)       | Ref                                      | Ref                              |
| 1–10                                | 102 (7.91)     | 235 (17.27)       | 1.22 (0.89–1.67)                         | 1.08 (0.78–1.49)                  |
| 11–19                               | 87 (6.75)      | 133 (9.77)        | 1.91 (1.34–2.70)                         | 1.50 (1.04–2.17)                  |
| 20–39                               | 260 (20.17)    | 216 (15.87)       | 3.60 (2.75–4.72)                         | 2.29 (1.71–3.07)                  |
| 40–49                               | 159 (12.34)    | 78 (5.73)         | 6.51 (4.62–9.19)                         | 3.83 (2.65–5.54)                  |
| 50 or more                          | 511 (39.64)    | 178 (13.08)       | 10.26 (7.87–13.39)                       | 3.80 (2.28–6.32)                  |
| **Alcohol use status**              |                |                   |                                          |                                  |
| Never-drinker                       | 121 (9.42)     | 289 (21.28)       | Ref                                      | Ref                              |
| Ex-drinker                          | 440 (34.24)    | 318 (23.42)       | 3.08 (2.33–4.07)                         | 1.64 (1.20–2.25)                  |
| Current drinker                     | 724 (56.43)    | 751 (55.30)       | 1.92 (1.49–2.48)                         | 1.28 (0.95–1.71)                  |
| Missing                             | 4 (0.31)       | 3 (0.22)          |                                          |                                  |
| **Total alcohol consumption (ml of ethanol)** |  |  |  |  |
| Never-drinker                       | 121 (9.39)     | 289 (21.23)       | Ref                                      | Ref                              |
| Up to 11,232                        | 57 (4.42)      | 160 (11.76)       | 0.78 (0.53–1.15)                         | 0.69 (0.46–1.05)                  |
| 11,232–204,469                      | 231 (17.92)    | 404 (29.68)       | 1.40 (1.07–1.89)                         | 1.12 (0.82–1.53)                  |
| 204,469–927,946                     | 315 (24.44)    | 320 (23.51)       | 2.62 (1.96–3.49)                         | 1.69 (1.22–2.32)                  |
| 927,946, and greater                | 565 (43.83)    | 188 (13.81)       | 8.84 (6.45–12.13)                        | 3.69 (2.59–5.24)                  |
| Missing                             | 82 (6.36)      | 45 (3.30)         |                                          |                                  |
| **Smokeless tobacco use (chew and/or snuff)** |  |  |  |  |
| Never                              | 1,063 (82.47)  | 1,182 (86.85)     | Ref                                      | Ref                              |
| Ever use of chew of snuff           | 226 (17.53)    | 179 (13.15)       | 1.32 (1.05–1.66)                         | 1.03 (0.79–1.33)                  |
| **Environmental tobacco exposure (home and work)** |  |  |  |  |
| None                                | 142 (11.03)    | 222 (16.32)       | Ref                                      | Ref                              |
| Cigarettes, cigars or pipe          | 1,145 (88.97)  | 1,138 (83.68)     | 1.76 (1.38–2.25)                         | 0.97 (0.73–1.28)                  |
| Missing                             | 2 (0.15)       | 1 (0.07)          |                                          |                                  |
| **History of any Cancer in first-degree relative** |  |  |  |  |
| No                                  | 522 (40.50)    | 573 (42.10)       | Ref                                      | Ref                              |
| Yes                                 | 767 (59.50)    | 788 (57.90)       | 1.30 (1.10–1.54)                         | 1.33 (1.10–1.61)                  |
| **Oral health factors**             |                |                   |                                          |                                  |
| Self-reported tooth mobility        |                |                   |                                          |                                  |
| No                                  | 801 (62.14)    | 1,048 (77.00)     | Ref                                      | Ref                              |
| Yes                                 | 372 (26.12)    | 311 (22.85)       | 2.17 (1.80–2.60)                         | 1.48 (1.20–1.83)                  |
| Missing                             | 10 (4)         | 4                 |                                          |                                  |
$50,000 had more than double the odds of SCCHN [OR 2.47 (1.69–3.25) $ p$ interaction < 0.001]. We observed a statistically significant interaction between smoking status and education level ($p$ interaction 0.009), and for smoking status and insurance type ($p$ interaction 0.011). Current smokers with less than a high school education had seven times the odds of never-smokers with some college education [OR 7.38 (5.03–9.73)]. Current smokers who attended some college or more were at nearly 2.5 times the odds of SCCHN than never-smokers with some college education [OR 2.49 (1.85–3.12)].

Current smokers with Medicaid/Medicare had the greatest odds of SCCHN compared to never-smokers with private health insurance [OR 3.26 (2.27–4.26)]. In contrast, current smokers with private insurance had two times the odds of SCCHN compared to never-smokers with private insurance [OR 2.68 (1.92–3.45)].

Although no evidence of interaction was observed between duration of cigarette smoking and SES ($p$ interaction: 0.24, 0.16, and 0.14 for income, education, and insurance, respectively) a suggestive pattern exists at the highest categories of smoking duration and income, similar to the income contrast for current smokers. Compared to never-smokers making more than $50,000 per year, the OR for smoking cigarettes for 40 or more years and having an income less than $20,000 was 5.52 (3.74–7.29)
(Supplemental Table 2), which was of greater magnitude than for individuals with 40 or more years of smoking history with an income greater than $50,000 [OR 3.40 (2.12–4.69)]. Similarly, smoking 40 or more years and having less than high school education was associated with nearly seven times the odds of SCCHN [OR 6.91 (4.61–9.21)]; for those in the same smoking category with some college education or more, the odds ratio was 3.92 (95% CI 2.67–5.17) (Supplemental Table 2). There was no clear pattern of interaction between smokeless tobacco by SES (Supplemental Table 3).

Table 5 presents the interaction between alcohol consumption by SES variables. The models showed evidence of multiplicative interaction between currently drinking alcohol and having lower income or fewer years of education (p values for interaction: 0.0693 and 0.0269, respectively). Current drinkers with incomes less than $20,000 were at nearly three times the odds of SCCHN compared to never-drinkers with income less than $20,000 (OR 2.91; 95% CI 2.05–3.78), while current drinkers with incomes greater than $50,000 had a less pronounced OR [1.28 (0.97–1.58)]. Individuals who had the lowest income and who drank the most alcohol, corresponding to approximately 25 drinks per week for 50 years, had nearly six times the odds of SCCHN compared to never-drinkers in the highest income tertile [OR 5.85 (3.74–7.96)] (Supplemental Table 4). This is greater than for those individuals with the same drinking history but an annual household income greater than $50,000 [OR 3.44 (1.98–4.90)]. Individuals with less than high school education and the highest category of alcohol consumption had five times the odds of SCCHN [OR 5.25 (3.27–7.96)], while individuals with some college education and the same drinking history having three times the odds [OR 2.95 (1.92–3.99)]. However, we found no evidence of interaction between the three SES variables and total grams of alcohol consumption (p values for interaction: 0.47, 0.54, and 0.60 for interaction with income, education, and insurance, respectively).

The oral health variables, history of loose permanent tooth, and prior routine dental visit, were explored separately (Supplemental Table 5). Neither oral health variable modified risk factor associations (p values for interaction of loose tooth: 0.96, 0.14, 0.90 with income, education, and insurance, respectively; p value for interaction of routine dental visit: 0.80, 0.66, 0.93 with income, education, and insurance, respectively).

Table 6 presents the odds of SCCHN across levels of income, education, and insurance, stratified by HPV status. HPV-negative individuals with an income less than $20,000 were at nearly two times greater odds of SCCHN development than HPV-negative individuals with incomes greater than $50,000 [OR 1.84 (1.09–3.10)]. HPV-positive individuals in the same income category, less than $20,000, had slightly lower odds [OR 1.35 (0.78–2.35)]. Increasing years of education was associated with decreased risk of SCCHN for both HPV-positive and HPV-negative individuals. However, these models are only based on a subset of the cases who were tested for HPV, therefore are more imprecise and

| Table 4 Interaction between ever-smoking cigarettes and SES variables (n=2,420: 1,153 cases, 1,267 controls) |
| --- | --- | --- | --- | --- |
| | Never-smoker (n=651) | Ex-smoker (N=856) | Current smoker (N=913) | p Interaction |
| Income | | | | <0.001 |
| > $50,000 | 1 (Ref) | 1.17 (0.84–1.50) | 2.47 (1.69–3.25) |
| $20,000–$50,000 | 0.83 (0.52–1.14) | 1.28 (0.94–1.62) | 3.77 (2.77–4.78) |
| < $20,000 | 0.84 (0.43–1.24) | 2.11 (1.39–2.85) | 5.11 (3.61–6.61) |
| Education | | | 0.09 |
| Some college and above | 1 (Ref) | 1.30 (0.98–1.62) | 2.49 (1.85–3.12) |
| High school graduate | 0.93 (0.55–1.13) | 1.53 (1.10–2.00) | 4.45 (3.14–5.78) |
| Less than high school | 0.91 (0.38–1.44) | 2.09 (1.36–2.81) | 7.38 (5.03–9.73) |
| Insurance type | | | 0.011 |
| Private | 1 (Ref) | 1.30 (0.93–1.67) | 2.68 (1.92–3.45) |
| Medicaid/Medicare | 0.47 (0.26–0.67) | 1.09 (0.76–1.42) | 3.26 (2.27–4.26) |
| None | 1.03 (0.19–1.88) | 1.40 (0.37–2.43) | 2.05 (1.25–2.85) |
| Other | 0.89 (0.46–1.32) | 1.03 (0.67–1.40) | 4.36 (2.43–6.29) |

*Adjusted for matching factors plus total alcohol consumption, oral health parameters, smokeless tobacco, family history of cancer, SES factors: income, education, insurance type (other than the of parameter interest)*
are only suggestive. There were no patterns observed for insurance.

Interaction between smoking and drinking status by SES was also explored after additional stratification by HPV status (Supplemental Tables 6 and 7). Among HPV-negative cases, current smokers with an income less than $20,000 were at 10 times the odds of SCCHN when compared to never-smokers with high income [OR 10.76 (6.73–14.79)]. This effect of smoking is higher than in patients with HPV-positive tumors in the same income stratum [OR 1.89 (0.84–2.93)]. However, there was no evidence of interaction (p value for interaction: 0.53 and 0.19 for HPV negative and positive, respectively). A similar trend was seen for current smokers with the lowest education level, though there was no statistically significant evidence of interaction (p values for interaction: 0.15 and 0.87 in HPV negative and positive, respectively). We did not observe interaction between SES and alcohol use when stratified by HPV status.

In a sensitivity analysis, the original insurance category, containing both Medicare and Medicaid, was subdivided to explore the individual effects. Medicaid was found to be more highly associated with SCCHN development compared to Medicare, although the Medicare results are imprecise. [OR 1.65 (0.91–2.54) and OR 0.74 (0.46–1.26) in Medicaid and Medicare, respectively]. Current smokers with Medicaid had nearly eight times the odds of SCCHN development compared to never-smokers with private health insurance [OR 7.90 (1.09–14.72)], which was a stronger association than observed for those with Medicare [OR

Table 5 Interaction between ever-drinking alcohol and SES variables (n = 2,420: 1,153 cases, 1,267 controls)  

| Income            | Never-drinker | Ex-drinker | Current drinker | p Interaction |
|-------------------|---------------|------------|-----------------|---------------|
|                   | N=390 (114 cases, 276 controls) | N=678 (396 cases, 282 controls) | N=1,352 (643 cases, 709 controls) |               |
|                   | OR (95% CI)   | OR (95% CI) | OR (95% CI) |               |
| > $50,000         | 1 (Ref)       | 2.16 (1.37–2.95) | 1.28 (0.97–1.58) | 0.069 |
| $20,000–$50,000   | 1.25 (0.75–1.75) | 1.71 (1.24–2.17) | 1.62 (1.24–1.99) |               |
| < $20,000         | 1.21 (0.66–1.76) | 2.52 (1.73–3.32) | 2.91 (2.05–3.78) |               |
| Education         |               |            |                 | 0.027 |
| Some college and above | 1 (Ref) | 1.65 (1.17–2.14) | 1.04 (0.82–1.26) |               |
| High school graduate | 0.82 (0.46–1.18) | 1.66 (1.11–2.19) | 1.78 (1.33–2.27) |               |
| Less than high school | 1.29 (0.66–1.91) | 2.19 (1.52–2.87) | 2.69 (1.80–3.58) |               |
| Insurance type    |               |            |                 | 0.149 |
| Private           | 1 (Ref)       | 1.91 (1.28–2.54) | 1.56 (1.17–1.95) |               |
| Medicaid/Medicare | 0.93 (0.53–1.33) | 1.72 (1.21–2.22) | 1.37 (0.99–1.75) |               |
| None              | 1.04 (0.20–2.06) | 0.87 (0.40–1.35) | 1.97 (1.15–2.80) |               |
| Other             | 1.24 (0.54–1.94) | 2.34 (1.33–3.34) | 1.51 (1.04–2.00) |               |

Table 6 Risk of SCCHN by SES variables, stratified by HPV status  

| p16 status | Fully adjusted |  
|------------|----------------|
| p16 status | Never-drinker | Ex-drinker | Current drinker | p Interaction |
| Positive   | N=192\(^b\) | N=242\(^b\) | N=192\(^b\) | N=242\(^b\) |  
| OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |  
| Income     |               |            |                 |               |  
| > $50,000  | 1 (Ref)       | 1 (Ref)    | 1 (Ref)         | 1 (Ref)       |  
| $20,000–$50,000 | 1.22 (0.75–1.67) | 1.12 (0.72–1.74) | 1.12 (0.72–1.74) | 1.12 (0.72–1.74) |  
| < $20,000  | 1.35 (0.78–2.35) | 1.84 (1.09–3.10) | 1.84 (1.09–3.10) | 1.84 (1.09–3.10) |  
| Education  |               |            |                 |               |  
| Some college and above | 1 (Ref) | 1 (Ref) | 1 (Ref) | 1 (Ref) |  
| High school graduate | 1.07 (0.71–1.62) | 1.74 (1.15–2.62) | 1.74 (1.15–2.62) | 1.74 (1.15–2.62) |  
| Less than high school | 1.48 (0.87–2.51) | 2.12 (1.31–3.40) | 2.12 (1.31–3.40) | 2.12 (1.31–3.40) |  
| Insurance type | Private | 1 (Ref) | 1 (Ref) | 1 (Ref) | 1 (Ref) |  
| Medicaid/Medicare | 0.77 (0.46–1.30) | 0.92 (0.57–1.51) | 0.92 (0.57–1.51) | 0.92 (0.57–1.51) |  
| None       | 0.85 (0.45–1.62) | 0.72 (0.40–1.31) | 0.72 (0.40–1.31) | 0.72 (0.40–1.31) |  
| Other      | 0.85 (0.50–1.45) | 1.15 (0.68–1.97) | 1.15 (0.68–1.97) | 1.15 (0.68–1.97) |  

\(^a\)Adjusted for matching factors plus duration of cigarette smoking, oral health parameters, smokeless tobacco, family history of cancer, environmental tobacco smoke, SES factors: income, education, insurance type (other than the of parameter interest)

\(^b\)Compared to 1,267 controls
It has been suggested that the association between fewer years of education and/or low income and disease development operate through pathways related to behavioral lifestyle factors or psychosocial factors [22]. Krieger et al. examined multiple theories surrounding the interaction of the individual with the environment, political system, and health and suggested that interactions between all three may lead lower SES groups to be at higher risk for disease [22]. It is possible that this interplay between environment and behavioral factors underlies the increased odds of SCCHN in our study population.

The independent effects of SES could be further explained by residual confounding or other unmeasured risk factor exposures, and misclassification of SES. It is unlikely that there are unmeasured confounding SCCHN risk factors because the etiology of SCCHN has been thoroughly investigated. Potential contributors to the modification of risk factors by socioeconomic status include unmeasured factors such as differing ways cigarette smoke is inhaled, type of cigarette smoked, and measurement errors in reporting of tobacco and alcohol use. Some variation in the effect of SES may be due to measurement error. In our study, each SES variable was classified into three to four categories, possibly resulting in heterogeneity within categories after collapsing information on income, education, or insurance. Additionally, the questionnaire collected income data in categories rather than asking for a fixed amount. Often individuals’ income or health insurance will vary over a lifetime; however for this study, data on the income and insurance type were only collected on the date of interview. We opted to not create an aggregate SES index due to prior literature suggesting the integration of different and complex SES factors could lead to a dilution of data quality [23]. SES is a complex concept and measurement by three variables may not capture all dimensions.

Our study is among the largest individual population-based studies of head and neck cancer conducted in the United States. The population-based design gives us more confidence that our results are generalizable. The questionnaire covered an extensive range of exposures and risk factors, only some of which are discussed in this paper. Additionally, this study is unique in its high proportion of black participants. Other studies of SCCHN have been predominately non-Hispanic whites. In analyzing the effects of SES, it is imperative to include diversity in both race and income. Although the number of African American participants in our study is larger than prior studies, the relatively small sample size of African Americans led to very imprecise estimates in the three-way interaction between race, SES, and known risk factors.

We have opted to not account for multiple comparisons. Given that our analysis is the first to examine this research question, and that we have provided specific a
priori hypotheses including interaction, we are providing a broader interpretation of results with a focus on the strength of association and precision of the effect measures [24, 25].

As socioeconomic status becomes more widely recognized as a pertinent factor in SCCHN etiology and prognosis, more measures of socioeconomic status should be collected, such as SES over the life course, and family size and household composition to increase comprehensiveness and precision of socioeconomic status measurement. Furthermore, prior research suggests that SES factors measured should be studied at not only the individual level but also the contextual and neighborhood level in order to better characterize socioeconomic position [26]. Additionally, future studies should attempt to fully integrate race and ethnicity information, as prior research has demonstrated that the effects of race cannot be fully explained by differences in consumption of tobacco and alcohol between races [27]. In addition, more research is needed on differences in smoking behavior, cigarette type, and access to cessation counseling among different socioeconomic classes.

Given that current smokers and drinkers with lower education and lower income are at significantly higher risk for SCCHN than current smokers and drinkers in higher-income groups, it is important to tailor preventative and interventional measures to these groups. Clinicians should be intimately aware of the patient population they are serving and think of earlier intervention in smoking and drinking for those at higher risk, particularly cessation. Similarly, patient education on SCCHN may be more beneficial if targeted to these high-risk groups. As routine dental visits were found to be protective against SCCHN development and showed increased protection and interaction even within the lowest SES categories, clinicians may consider discussing dental visits with their patients. Ultimately, upstream or distal attempts to decrease poverty, increase educational attainment, and provide adequate health insurance may have increased health benefits beyond that of smoking and drinking cessation.

Funding This study was funded by the following Grants: National Cancer Institute, Award Number: R01-CA90731, Recipient: Andrew Olshan, PhD. Rotary Foundation, Rotary International Global Grant Scholarship, Recipient: Gaelen Stanford-Moore, MD MPhil.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Koyanagi YN et al (2016) Cigarette smoking and the risk of head and neck cancer in the Japanese population: a systematic review and meta-analysis. Jpn J Clin Oncol 46(6):580–595
2. Hashibe M et al (2007) Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. JNCI 99(10):777–789
3. Blot WJ et al (1988) Smoking and Drinking in relation to oral and pharyngeal cancer. Cancer Res 48:3282–3287
4. Elwood JM, Pearson JCG, Skippen DH, Jackson SM (1984) Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. Int J Cancer 34(5):603–612
5. Centers for Disease Control and Prevention (2013) Smoking and tobacco use; data and statistics; tables, charts, and graphs; trends in current cigarette smoking. cdc.gov. https://www.cdc.gov/tobacco/data_statistics/tables/charts/cig_smoking/. Accessed 02 Mar 2017
6. Vigneswaran N, Williams MD (2014) Epidemiologic trends in head and neck cancer and aids in diagnosis. Oral Maxillofac Surg Clin North Am 26(2):123–141
7. Guha N et al (2007) Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case-control studies. Am J Epidemiol 166(10):1159–1173
8. Mazul AL et al (2017) Oral health and human papillomavirus-associated head and neck squamous cell carcinoma. Cancer 123(1):71–80
9. Vigneswaran N, Williams MD (2014) Epidemiologic trends in head and neck cancer and aids in diagnosis. Oral Maxillofac Surg Clin North Am 26(2):123–141
10. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LMD (2008) Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer 122(12):2811–2819
11. Conway DI et al (2015) Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries. Int J cancer 136(5):1125–1139
12. Conway DI et al (2010) Socioeconomic factors associated with risk of upper aerodigestive tract cancer in Europe. Eur J Cancer 46(3):588–598
13. Andersen ZJ, Funch Lassen C, Clemmensen IH (2008) Social inequality and incidence of and survival from cancers of the mouth, pharynx and larynx in a population-based study in Denmark. Eur J Cancer 44:1950–1961
14. Whittemore AS (1989) Colorectal cancer incidence among Chinese in North America and the people’s republic of China: variation with sex, age and anatomical site. Int J Epidemiol 18(3):563–568
15. Diveris K et al (2010) Oral health and risk for head and neck squamous cell carcinoma: the Carolina Head and Neck Cancer Study. Cancer Causes Control 21(4):567–575
16. Lassen P et al (2014) Impact of HPV-associated p16-expression on radiotherapy outcome in advanced oropharynx and non-oropharynx cancer. Radiother Oncol 113(3):310–316
17. D’Souza G et al (2016) Effect of HPV on head and neck cancer patient survival, by region and tumor site: A comparison of 1362 cases across three continents. Oral Oncol 62:20–27
18. NIH, What is a standard drink? | National Institute on Alcohol Abuse and Alcoholism (NIAAA). https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink. Accessed 28 June 2017
19. Greenland S, Robins James (1998) Empirical-bayes adjustments for multiple comparisons are sometimes useful. Am J Epidemiol 147(9):801–806
20. Wyss AB et al (2016) Smokeless tobacco use and the risk of head and neck cancer: pooled analysis of US studies in the INHANCE Consortium. Am J Epidemiol 184(10):703–716
21. Hashibe M et al (2009) Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomark Prev 18(2):541–550
22. Krieger N (2001) Theories for social epidemiology in the 21st century: an ecosocial perspective. Int J Epidemiol 30(4):668–677
23. Shavers VL (2007) Measurement of socioeconomic status in health disparities research. J Natl Med Assoc 99(9):1013–1023
24. Lash TL (2017) The harm done to reproducibility by the culture of null hypothesis significance testing. Am J Epidemiol 186(6):627–635
25. Stang A, Poole C, Kuss O (2010) The ongoing tyranny of statistical significance testing in biomedical research. Eur J Epidemiol 25(4):225–230
26. Krieger N, Williams DR, Moss NE (1997) Measuring social class in us public health research: concepts, methodologies, and guidelines. Annu Rev Public Health 1938(16):341–378
27. Stingone JA, Funkhouser WK, Weissler MC, Bell ME, Olshan AF (2013) Racial differences in the relationship between tobacco, alcohol, and squamous cell carcinoma of the head and neck. Cancer Causes Control 24(4):649–664