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Racial differences in the relationship between tobacco, alcohol, and the risk of head and neck cancer: Pooled analysis of US studies in the INHANCE Consortium

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Abstract

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There have been few published studies on differences between Blacks and Whites in the estimated effects of alcohol and tobacco use on the incidence of head and neck cancer (HNC) in the United States. Previous studies have been limited by small numbers of Blacks. Using pooled data from 13 US case-control studies of oral, pharyngeal, and laryngeal cancers in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, this study comprised a large number of Black HNC cases (n=975). Logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for several tobacco and alcohol consumption characteristics. Blacks were found to have consistently stronger associations than Whites for the majority of tobacco consumption variables. For example, compared to never smokers, Blacks who smoked cigarettes for >30 years had an OR=4.53 (95% CI=3.22–6.39), which was larger than that observed in Whites (OR=3.01, 95% CI=2.73–3.33; $p_{interaction}$ <0.0001). The ORs for alcohol use were also larger among Blacks compared to Whites. Exclusion of oropharyngeal cases attenuated the racial differences in tobacco use associations but not alcohol use associations. These findings suggest modest racial differences exist in the association of HNC risk with tobacco and alcohol consumption.

Keywords

head and neck cancer; alcohol; tobacco; cigarette smoking; African American; racial difference

INTRODUCTION

Head and neck cancers (HNC) include cancers of the oral cavity, pharynx and larynx, and account for more than half a million cases worldwide each year [1]. In 2014, HNC was the ninth most common incident cancer in the United States [2]. According to the American Cancer Society, over 61,000 individuals in the United States will be diagnosed with HNC in 2016 and approximately 13,000 deaths will be attributed to it this year [3]. It has been well documented that in the United States there are racial disparities in both HNC incidence and mortality [2]. The most pronounced racial difference in HNC incidence are found in laryngeal cancer. Data from the Surveillance Epidemiology and End Results (SEER) Program show age-adjusted incidence rates were highest among Black males at 12.1 per 100,000, compared to an incidence of 7.7 per 100,000 in White males [4]. Among women, the age-adjusted incidence rate was 2.3 per 100,000 among Blacks and 1.5 per 100,000 among Whites [4]. These incidence rates have remained relatively stable throughout the past decade despite changes in tobacco products and reductions in the prevalence of use [5]. This stability contrasts with the incidence rates of oropharyngeal cancer where the racial difference has reversed due to a rise in the incidence rate among White males. [6,7] Currently, the incidence rate for oropharyngeal cancer is higher among Whites (men= 8.0 and women= 1.8 per 100,000) compared to Blacks (men= 6.9 and women= 1.5/100,000) [7].

Tobacco and alcohol use are well-established risk factors for HNC [8,9]. There have been few studies published comparing the differences between Blacks and Whites in the estimated effects of alcohol and tobacco use and the incidence of head and neck cancer (HNC) in the United States. A previous study using data from a North Carolina (2002–2006) study with 1,340 cases (351 Black cases) of oral, pharyngeal and laryngeal cases, showed

that among individuals who have a history of cigarette smoking, Blacks are at a higher risk for HNC compared to Whites [5]. An earlier US multicenter study (194 Black cases), found similar cigarette smoking odds ratios for oral and pharyngeal cancer for Whites and Blacks, but Blacks had increased odds ratios for most levels of alcohol consumption [10]. Utilizing U.S. study data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, the current study expands upon previous work by including the largest study sample of Black HNC cases analyzed to date. This will allow for more refined and precise estimate of the association between tobacco and alcohol use and HNC by race.

METHODS

Study Design

The INHANCE Consortium has pooled data from 35 case-control studies of HNC from around the world (data version 1.5) [11]. Because our focus is on the disparity observed in US populations, all studies taking place outside of the United States were excluded from this analysis. Due to small numbers in other race and ethnicity categories, the dataset was further restricted to include only non-Hispanic Whites and Blacks. Similar to a recent INHANCE analysis of smokeless tobacco [12], individuals with missing data on sex, age, race, subtype of cancer (38 cases and 7 controls) or data on duration of cigar smoking, or duration of pipe smoking (265 cases and 189 controls) were excluded from all analyses because we included terms for these characteristics as covariates in all of our models. Additionally, individuals with missing information on intensity of ethanol intake (119 cases and 157 controls) were excluded from models estimating associations with cigarette smoking characteristics, and individuals with missing information on cigarette pack-years (81 cases and 80 controls) were excluded from models estimating associations with alcohol consumption characteristics. We also excluded the Buffalo and HOTSPOT studies [13,14] from this analysis because they each contained fewer than 5 Black cases.

Therefore, the final dataset for this analysis is comprised of 13 studies: 2 conducted in Seattle (LEO, and 1985–1995), North Carolina (hospital-based 1994–1997, and population-based 2002–2006), New York (Memorial Sloan Kettering 1992–1994, and multicenter 1981–1990), and 1 each conducted in Iowa (1993–2006), Tampa (1999–2003), Los Angeles (1999–2004), Houston (2001–2006), Boston (1999–2003),, Baltimore (2000–2005), and a US multicenter study (Atlanta, Los Angeles, New Jersey, and San Francisco 1983–1984).

A majority of the studies used in this analysis were hospital-based (n=8 of 13), and most studies selected controls to be frequency-matched to cases (n=10) on age and sex. Descriptions of studies and more detailed variable descriptions have been previously reported [7,8].

HNC cases were categorized by tumor site according to the International Classification of Disease for Oncology Version 2 or the International Classification of Diseases Version 9 or 10, depending on the original study. Incident cancers of the oral cavity (C00.3-C00.9, C02.0-C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0-C06.2, C06.8, C06.9)), oro-pharynx (C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2-C10.4, C10.8, C10.9), oral cavity or pharynx overlapping or not otherwise specified

(C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, C14.8), larynx (C10.1, C32.0-C32.3, C32.8-C32.9), and hypopharynx (C12.9, C13.0-C13.2, C13.8, C13.9) were included.

Informed consent and institutional review board was obtained at each study site. All identifying information was removed before data were pooled.

Statistical Analysis

Prior to receiving the data for this analysis, INHANCE staff pooled and harmonized the data across studies. Logistic regression models were used to (1.) test the null hypothesis of no race-alcohol and no race-tobacco interactions using a likelihood ratio test (LRT), and (2.) estimate the alcohol- and tobacco-use effects on HNC separately for Blacks and Whites. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for ever cigarette smoking, frequency of cigarette smoking (cigarettes per day), the duration of cigarette smoking (in years), and the cumulative use of cigarette smoking (pack-years) compared with never cigarette smokers, using unconditional logistic regression. Those who smoked fewer than 100 cigarettes in in their lifetime were considered never smokers. Those who responded that they ever smoked were then asked about their average frequency of use. Former smokers reported having stopped smoking cigarettes for at least one year. ORs were also calculated for ever alcohol use, number of drinks per day, amount of alcohol per day (in mL), and duration of alcohol use. The definition for ever alcohol drinkers varied by individual study definitions. When participants responded that they ever drank alcohol, they were then asked about their frequency of use. Former drinkers reported having stopped drinking for at least one year. Categories of these variables were chosen to correspond to previous INHANCE and other literature on these risk factors [5,15].

Likelihood ratio tests (LRTs) were used to test the null hypothesis that the adjusted OR for the tobacco or alcohol association with HNC was the same for Blacks and Whites. To do this, an interaction term between race and each cigarette smoking or alcohol consumption variable was included in the respective logistic regression models, which were then compared to the respective models that did not include the interaction term. We compared the likelihood scores of the two models and calculated a p-value (degrees of freedom = number of categories within each characteristic- 1). Race was found to be an effect measure modifier on the association between cigarette smoking and alcohol consumption characteristics and HNC (see Tables 2 and 3 for LRT p-values). Therefore it was decided that all associations would be shown separately for Blacks and Whites. Sparse data by race prevented the investigation of stable 3-way interactions between race, sex, and exposure to cigarette smoking, and alcohol consumption.

Covariates included in the models were identified as confounders *a priori* from our directed acyclic graph (DAG). ORs were adjusted for sex, age (continuous), educational level (no education or less than junior high, some college, high school graduate, vocational or some college, and college graduate or postgraduate; with missing values imputed for 17 individuals), duration of cigar smoking (years, continuous), duration of pipe use (years, continuous), and study center. For cigarette smoking variables, odds ratios were also adjusted for frequency of alcohol use (mL of ethanol per day; categorical variable: never drinker, 0 to ≤1, 1 to ≤3, 3 to ≤ 8, 8 to ≤ 18, 18 to ≤40, 40 - ≤75, 75 to ≤115, 115 to ≤ 155,

and >155). Similarly, for alcohol variables, odds ratios were also adjusted for the cumulative use of cigarette smoking (pack-years, continuous).

Infection with human papilloma virus (HPV) is a strong risk factor for oropharyngeal cancer. We did not have data on HPV infection within the pooled study sample. Therefore, due to concern that inability to account for HPV infection would confound the estimated effects of tobacco and alcohol use on HNC, we conducted a sensitivity analysis that excluded cases of oropharyngeal cancer. We also conducted a hierarchical logistic regression with study center as a random effect variable and found estimates of association similar to fixed effect estimates. Therefore, only fixed effect estimates will be presented. All analyses were performed using SAS version 9.4.

RESULTS

The majority of the study population was White (87.1% cases and 90.0% controls). A total of 975 Black cases and 953 Black controls were included in the analysis. Approximately two-thirds of the cases and controls were male and about half of the study participants were between the ages of 50–64 (50.4% of cases and 48.3% of controls, Supplemental Table 1). Most of the participants included in this analysis were from the New York Multicenter Center (18.9% cases and 16.9% controls), the North Carolina (2002–2006) study (17.2% cases and 14.3% controls), and the US Multicenter study (14.0% cases and 12.4% controls; Supplemental Table 1). These general patterns remained when the population was further stratified by race (Table 1). The majority of Black cases were from the North Carolina (2002–2006) study (35.2% cases and 27.5% controls) and US Multicenter (19.8% cases and 21.2% controls) studies.

The results for cigarette smoking are presented in Table 2. In Whites, the adjusted OR was 1.09 (95% CI= 0.98–1.20) in former smokers compared to never smokers. This is similar to the OR in Black former smokers (OR=1.25, 95% CI=1.87–3.39). For current smokers, the adjusted odds ratio was also similar for Blacks and Whites (OR=3.82, 95% CI=2.77–5.27) and (OR=3.39, 95% CI=3.07–3.75), respectively. We found higher ORs among Blacks compared to Whites when other measures of cigarette smoking were examined. For example, among Blacks who smoked between 21 and 30 cigarettes a day, the OR was 5.11 (95% CI= 3.20–8.17), whereas the OR in Whites was 2.65 (95% CI= 2.33–3.01) and for more than 30 cigarettes per day the ORs were 4.76 (95% CI=2.94–7.70) and 2.66 (95% CI=2.37–2.99), respectively. We saw consistently higher odds ratios at each pack-years level for Blacks compared to Whites. We found that Blacks with >30 pack-years of cigarette exposure had an OR of 5.27 (95% CI= 3.68–7.55); White individuals had an OR of 2.83 (95%CI=2.57–3.12). The ORs for HNC decreased as the number of years since quitting increased for both races (Table 2). The estimates of association were similar between the groups, although the estimates were more imprecise among Blacks.

The adjusted ORs for alcohol consumption variables were higher in Blacks compared to Whites (Table 3). For example, an OR of 1.57(95% CI=1.42–1.73) was found for Whites who were ever drinkers compared to an OR of 2.85 (95% CI=2.08–3.91) among Blacks. An OR of 4.46 (95% CI=3.80–5.25) was observed in Whites who drank more than 5 drinks per

day compared to an OR of 7.70 (95% CI=4.92–12.06) for Blacks. Drinking for more than 40 years had an OR of 1.78 (95% CI=1.58–2.01) for Whites and 3.27 (95% CI=2.20–4.87) for Blacks.

We found a similar pattern of differences between races for the association with smoking after stratification by tumor site (Supplemental Tables 2–3). The strongest associations were found in laryngeal cancer in both Whites and Blacks, with Blacks generally have larger adjusted ORs. For laryngeal cancer, among Whites the OR for the association between smoking cigarettes for more than 30 years, the OR was 12.1 (95% CI= 9.30–15.7) compared to never smokers. Among Blacks, the corresponding OR was 17.9 (95% CI= 8.23–39.1). Similar or elevated ORs were calculated for Blacks compared to Whites for all other tumor sites.

For most tumor sites there was little difference between groups for the association with alcohol; however, some differences were noted but sparse data for Blacks limits interpretation. For example, considering oropharynx cancer, the odds ratio for Whites who drank for ≥ 30 years was 1.81 (95% CI= 1.59–2.06) and 4.60 (95% CI= 2.79–7.59) for African-Americans.

After exclusion of oropharyngeal cancer cases in the sensitivity analyses, for some of the smoking characteristics Blacks appear to still be at an increased risk of cancer, however, the differences were attenuated compared to the original analysis (Table 2). This can very clearly be seen among former smokers where the ORs were almost identical for Whites and Blacks (OR=1.14, 95% CI= 1.01–1.29; OR=1.13, 95% CI= 0.75–1.71). For smoking frequency, smoking duration and cumulative smoking, Blacks had a higher odds ratio for almost every category, although the magnitude was attenuated with this exclusion and the precision of the estimates for Blacks was slightly increased. For example, Whites who accumulated more than 30 pack-years of smoking had an OR=3.45 (95% CI= 3.08–3.86), whereas Blacks had a slightly higher odds ratio OR=4.87 (95% CI= 3.27–7.24). Results for alcohol intake did not change drastically upon exclusion. Overall, Blacks had similar, or slightly higher, estimates of association compared to Whites. For example, Whites who were current drinkers had an OR=1.72 (95% CI= 1.49–2.00) compared to Blacks who had an OR= 2.41 (1.55–3.74).

DISCUSSION

Most of the previous studies of the association of HNC with cigarette smoking and alcohol use in Blacks have been limited by small numbers. The current study includes the largest sample of Blacks to date (975 cases and 953 controls), thus allowing for more precise estimates of association in this population.

The adjusted ORs associated with alcohol consumption variables were similar, or slightly higher, in Blacks compared to Whites. This is consistent with what was observed in the analysis of the North Carolina (2002–2006) study, where Blacks were found to have greater odds of disease for each level of total alcohol consumption measured [5]. In the US Multicenter study of oral and pharyngeal cancer, Blacks were found to have approximately

two times higher ORs than Whites in each frequency of total alcohol consumption [10]. When we stratified by race and only look at oropharyngeal cases in our study, we see similar results (Supplemental Tables 2–3). The reasons for these differences by race are unknown but could include differences in alcohol metabolism or differences in background incidence of HNC by races [5, 16].

We also found differences in odds ratios upon stratification by both race and tumor site. Overall, Blacks had higher estimates in the majority of head and neck tumor sites for both cigarette smoking and alcohol intake. The strongest estimates of association for cigarette smoking characteristics were seen in laryngeal cancer, where Blacks were found to have higher estimates of association compared to Whites. Interestingly, Whites were found to have a higher effect estimates for hypopharyngeal cancer compared to Blacks, however this finding should be interpreted cautiously due to wide confidence intervals.

For oropharyngeal cancer, we found higher ORs for smoking among Blacks compared to Whites. This difference may reflect differing rates of HPV infection, a major risk factor for oropharyngeal cancer. Studies have shown that Blacks are less likely to have HPV-associated oropharyngeal cancer when compared to Whites [17, 18]. It has also been shown that HPV prevalence in oropharyngeal cancers has been increasing significantly among whites over time [19]. We did not have information on HPV status, so we were unable to directly evaluate the extent to which differences in the association between cigarette smoking and oropharyngeal cancer between races might be due to differences in the contribution of HPV infection. However, for all of the HNC sites we conducted a sensitivity analysis in which we excluded all oropharyngeal cancer cases (Table 2). Although the differences were attenuated compared to the original analysis, we continued to observe smoking associations that were stronger among Blacks compared to Whites. The results for alcohol intake characteristics did not change much upon exclusion of oropharyngeal cancer cases (Table 3).

In the present analysis, Blacks generally exhibited stronger estimates of association for higher intensity and duration of cigarette smoking and HNC. Several explanations have been offered to explain this disparity, including differences in the way that Blacks and Whites smoke cigarettes. Studies have shown that a greater proportion of Blacks prefer menthol cigarettes than Whites [20–22]. It has been hypothesized that the anesthetizing effect of menthol enables smokers to tolerate deeper or more frequent inhalations [23]. In fact, it has also been found that menthol smokers have appreciably larger puff volumes but the research on whether cotinine levels are also increased in menthol smokers is mixed [24]. However, a study by Wagenknecht et al. [25, 26] showed similar serum levels of thiocyanate in Blacks and Whites, a metabolite of cyanide that reflects tobacco product exposure after adjusting for number of cigarettes smoked per day. Some *in vitro* and *in vivo* studies have shown that menthol may alter metabolism of some tobacco carcinogens resulting in the potential for accumulation of these carcinogens [27]. Also, studies have not been able to show excess smoking-related cancer risk in mentholated compared to nonmentholated cigarette smokers [28–30]. Of particular relevance to HNC, the North Carolina (2002–2006) study showed lower odds of disease among menthol compared to nonmentholated cigarette smokers [5].

It has also been proposed that genetic differences in tobacco metabolism enzymes could explain the difference in HNC risks between Blacks and Whites. Blacks have higher frequencies of reduced functioning enzymes which are involved in tobacco carcinogen metabolism [31–39], which could result in Blacks being exposed to higher levels of carcinogen exposure when compared to Whites given the same reported consumption level [40, 41]. Even for subjects on the nicotine patch, Blacks were found to excrete less nicotine and cotinine compared to Whites, suggesting that differences in metabolism are not due to exposure to other components of tobacco smoke [42]. However, in comparison to cigarette smoking and alcohol consumption, any effect of a genetically determined metabolic difference by race would likely be small.

Another possible explanation is that Whites have a higher background incidence rate of HNC in non-smokers and non-drinkers (NSNDs). While there are few descriptive studies on HNC in NSNDs, they suggest that there are different clinicopathologic features including younger age, female sex, slightly higher prevalence of HPV infection, and higher prevalence of environmental tobacco exposure [43–45]. In the one study that reported data by race, there were equal numbers of Whites in the NSND group compared to the ever-smoker and ever-drinker (ESED), whereas there were double the number of Blacks in the ESED group compared to the NDNS group [45]. Due to the variability in study year and location, we did not calculate underlying incidence rates so we were unable to address this possible explanation in our analysis. Finally, it could be that risk factors other than smoking and drinking better explain HNC risk in Whites but not in Blacks, therefore resulting in the stronger associations seen in Blacks in this study.

The major strength of this study is the large number of Black cases and controls. This allowed for improved precision compared to previous studies on smoking and alcohol use among Blacks. It also allowed for the further stratification by tumor site. Another strength of this study is the availability of multiple smoking and alcohol consumption characteristics, which have been harmonized across INHANCE studies.

The current analysis includes pooled and harmonized data from both hospital-based and population-based studies. Hospital-based studies may be more vulnerable to selection bias through control selection. Retrospective recall of smoking and alcohol use could potentially lead to exposure misclassification; however, research has shown that individuals can accurately report current and past use of tobacco and alcohol products [46–48]. This study includes a small proportion of cases with non-squamous cell histologies (279 cases). These adenocarcinomas are not known to be associated with tobacco or alcohol exposure. This small proportion of cases (4.2%) is unlikely to affect the estimates presented. Additionally, there is the possibility of residual confounding in this analysis due to missing data on potential confounders such as HPV infection. Finally, even with the larger sample size, some estimates, especially with stratification by tumor site, are imprecise among Blacks.

In summary, this study more precisely estimate the association between cigarette smoking and alcohol use and HNC in Blacks in the United States. ORs for cigarette smoking and HNC were modestly higher among Blacks compared to Whites, while estimates of association of alcohol use and HNC were similar or slightly higher. After the exclusion of

oropharyngeal cases the differences by race for tobacco use remained but were attenuated; the alcohol use associations were not. The reason for these differences in risk by race are not known, but could possibly be due to differences in alcohol and tobacco metabolism, differing usage and cessation patterns by race. The fact that Blacks who smoke are at an increased risk of HNC is an important public health concern, because despite being more likely to attempt to quit than Whites, Blacks have lower likelihod of successfully quitting [49–51]. Future studies should further examine the basis for these racial differences and improve approaches to reduce tobacco use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic Characteristics of Head and Neck Cancer Cases and Controls by Race, INHANCE, 1981–2007

Characteristic		White				Black			
		Cases	%	Controls	%	Cases	%	Controls	%
Sex									
	Female	1897	28.8	2824	33.1	236	24.2	319	33.5
	Male	4702	71.3	5709	66.9	739	75.8	634	66.5
Age									
	17–39	283	4.3	479	5.6	36	3.7	84	8.8
	40–44	315	4.8	444	5.2	61	6.3	75	7.9
	45–49	591	9	753	8.8	154	15.8	118	12.4
	50–54	928	14.1	1217	14.3	182	18.7	170	17.8
	55–59	1198	18.2	1499	17.6	186	19.1	178	18.7
	60–64	1159	17.6	1393	16.3	156	16	126	13.2
	65–69	963	14.6	1260	14.8	102	10.5	106	11.1
	70–74	690	10.5	902	10.6	68	7	58	6.1
	75+	472	7.2	586	6.9	30	3.1	38	4
Education Level									
	Less than junior high school	384	5.8	308	3.6	120	12.3	64	6.7
	Some high school	1195	18.1	947	11.1	400	41	225	23.6
	High school graduate	1698	25.7	1803	21.1	232	23.8	178	18.7
	Vocational school, some college	2011	30.5	2890	33.9	189	19.4	321	33.7
	College graduate/postgraduate	1311	19.9	2585	30.3	34	3.5	165	17.3
Study Center									
	Baltimore	180	2.7	171	2	22	2.3	16	1.7
	Boston	445	6.7	572	6.7	25	2.6	23	2.4
	Houston	695	10.5	718	8.4	63	6.5	66	6.9
	Iowa	517	7.8	720	8.4	9	0.9	17	1.8
	Los Angeles	255	3.9	632	7.4	58	6	101	10.6
	MSKCC	93	1.4	137	1.6	8	0.8	8	0.8
	New York Multicenter	1290	20	1485	17.4	143	14.7	119	12.5

Characteristic		White				Black				
		Cases	%	Controls	%	Cases	%	Controls	%	
	North Carolina (1994–1997)	109	1.7	174	2	66	6.8	26	2.7	
	North Carolina (2022–2006)	960	14.6	1095	12.8	343	35.2	262	27.5	
	Seattle (1985–1995)	387	5.9	579	6.8	15	1.5	17	1.8	
	Seattle-Leo	613	9.3	522	6.1	21	2.2	13	1.4	
	Tampa	188	2.9	753	8.8	9	0.9	83	8.7	
	US Multicenter	867	13.1	975	11.4	193	19.8	202	21.2	
Tumor Site										
	Head and Neck (NOS)	6	0.1			0.00	0.00			
	Hypopharynx	333	5.1			91	9.3			
	Larynx	1270	19.3			239	24.5			
	Oral Cavity	2016	30.6			232	23.8			
	Oral/Pharynx (NOS)	688	10.4			118	12.1			
	Oro-pharynx	2286	34.5			295	30.3			

Table 2.

Cigarette Smoking Characteristics and Associations with Head and Neck Cancer Risk, INHANCE Consortium, 1981–2007

	White								Black								
Cigarette Use Characteristic	**Cases**	**%**	**Controls**	**%**	**Adjusted OR[a]**	**Adjusted 95% CI**	**Sensitivity Analysis Adjusted OR[a,e]**	**Sensitivity Analysis Adjusted 95% CI**	**Cases**	**%**	**Controls**	**%**	**Adjusted OR[a]**	**Adjusted 95% CI**	**Sensitivity Analysis Adjusted OR[a,e]**	**Sensitivity Analysis Adjusted 95% CI**	**LRT p-value[f]**
Cigarette Smoking																	
Never	1203	18.2	3308	38.8	1		1		93	9.6	372	39.0	1		1		<0.0001
Ever	5395	81.8	5224	61.2	1.79	1.65–1.95	2.08	1.88–2.30	880	90.4	581	61.0	2.52	1.87–3.39	2.47	1.77–3.45	
Missing	1		1						2		0						
Cigarette Smoking Status																	
Never	1203	18.2	3308	38.8	1		1		93	9.6	372	39.0	1		1		0.048
Former	1740	26.4	3358	39.4	1.09	0.98–1.20	1.14	1.01–1.29	173	17.8	281	29.5	1.25	0.87–1.80	1.13	0.75–1.71	
Current	3654	55.4	1866	21.9	3.39	3.07–3.75	4.18	3.72–4.70	707	72.7	300	31.5	3.82	2.77–5.27	3.89	2.71–5.58	
Missing	2		1						2		0						
Smoking Frequency[b]																	
Never	1203	18.2	3308	38.8	1		1		93	9.6	372	39.2	1		1		<0.0001
1–10	493	7.5	1121	13.2	1.08	0.95–1.23	1.05	0.90–1.24	198	20.5	251	26.5	1.58	1.11–2.24	1.48	1.00–2.20	
11–20	1817	27.6	2039	23.9	1.80	1.62–1.99	2.06	1.83–2.32	366	37.9	220	23.2	2.78	1.95–3.94	2.83	1.91–4.18	
21–30	1180	18.0	857	10.1	2.65	2.33–3.01	3.31	2.86–3.83	137	14.2	53	6.0	5.11	3.20–8.17	4.95	2.96–8.29	
>30	1880	28.6	1197	14.1	2.66	2.37–2.99	3.26	2.85–3.74	173	18.0	52	5.5	4.76	2.94–7.70	3.85	2.23–6.64	
Missing	26		11						8		5						
Smoking Duration[c]																	
Never	1187	18.1	3291	38.6	1		1		87	9.1	372	39.2	1		1		<0.0001
1–10	304	4.6	819	9.6	0.93	0.80–1.09	0.80	0.65–0.99	16	1.7	81	8.5	0.68	0.36–1.30	0.65	0.31–1.36	
11–20	408	6.2	970	11.4	1.00	0.87–1.15	1.14	0.96–1.36	47	4.9	99	10.4	1.35	0.83–2.21	1.33	0.76–2.32	
21–30	899	13.7	1209	14.2	1.51	1.34–1.70	1.70	1.47–1.96	196	20.5	148	15.6	2.37	1.60–3.52	2.11	1.35–3.30	
>30	3774	57.4	2228	26.2	3.01	2.73–3.33	3.57	2.18–4.01	612	63.9	249	26.2	4.53	3.22–6.39	4.14	2.84–6.04	
Missing	27		16						17		4						
Cumulative Smoking[d]																	
Never	1203	18.3	3308	38.9	1		1		93	9.7	372	39.2	1		1		0.016
1–10	430	6.6	1181	13.9	0.92	0.81–1.05	0.83	0.70–0.99	86	9.0	179	18.9	1.19	0.80–1.79	1.13	0.71–1.80	
11–20	398	6.1	792	9.3	1.19	1.03–1.38	1.30	1.09–1.55	112	11.7	129	13.6	1.66	1.10–2.52	1.73	1.08–2.76	

Cigarette Use Characteristic	White Cases	%	Controls	%	Adjusted OR[a]	Adjusted 95% CI	Sensitivity Analysis Adjusted OR[a,e]	Sensitivity Analysis Adjusted 95% CI	Black Cases	%	Controls	%	Adjusted OR[a]	Adjusted 95% CI	Sensitivity Analysis Adjusted OR[a,e]	Sensitivity Analysis Adjusted 95% CI	LRT p-value[f]
21–30	523	8.0	779	9.2	1.46	1.27–1.68	1.65	1.40–1.96	135	14.1	92	9.7	2.61	1.71–4.00	2.36	1.46–3.82	
>30	4007	61.1	2453	28.8	2.83	2.57–3.123	3.45	3.08–3.86	529	55.4	176	18.6	5.27	3.68–7.55	4.87	3.27–7.24	
Missing	38		20						20		5						
Years Since Quitting																	
Never Smoked	1203	18.2	3308	38.8	1		1		93	9.6	372	39.0	1		1		0.231
Current Smoker	3654	55.4	1866	21.9	3.61	3.27–3.99	4.41	3.93–4.96	707	72.7	300	31.5	4.10	2.96–5.68	3.93	2.72–5.67	
1–10	675	10.2	832	9.8	1.68	1.47–1.92	1.85	1.58–2.16	98	10.1	97	10.2	1.90	1.24–2.93	1.71	1.05–2.77	
11–20	508	7.7	1027	12.0	1.09	0.95–1.25	1.12	0.95–1.32	41	4.2	78	8.2	0.94	0.55–1.59	0.76	0.41–1.42	
21–30	329	5.0	847	9.9	0.84	0.72–0.98	0.84	0.62–1.02	19	2.0	59	6.2	0.78	0.40–1.49	0.88	0.43–1.78	
>30	227	3.4	652	7.6	0.73	0.61–0.88	0.76	0.62–0.95	15	1.5	47	4.9	0.67	0.32–1.38	0.51	0.22–1.20	
Missing	3		1						2		0						

[a] Odds ratios adjusted for age, sex, study center, educational level, frequency of alcohol use (mL of ethanol per day, continuous), duration of cigar smoking (years, continuous), and duration of pipe smoking (years, continuous).

[b] in cigarettes/day

[c] in years

[d] in pack-years

[e] Odds ratio and 95% CI calculated after exclusion of all oro-pharyngeal cancer cases

[f] This p-value reflects the LRT between the each cigarette smoking characteristic and race within all HNC

Table 3.

Alcohol Use Characteristic and Associations with Head and Neck Cancer Risk, INHANCE Consortium, 1981–2007

	White								Black								
Alcohol Use Characteristic	**%**	**Cases**	**Controls**	**%**	**Adjusted OR[a]**	**Adjusted 95% CI**	**Sensitivity Analysis Adjusted OR[a,f]**	**Sensitivity Analysis Adjusted 95% CI**	**Cases**	**%**	**Controls**	**%**	**Adjusted OR[a]**	**Adjusted 95% CI**	**Sensitivity Analysis Adjusted OR[a,r]**	**Sensitivity Analysis Adjusted 95% CI**	**LRT p-value[g]**
Alcohol Use[b]																	
Never	13.1	863	2028	23.8	1		1		70	7.2	273	28.7	1		1		0.0001
Ever	86.9	5730	6502	76.2	1.57	1.42–1.73	1.58	1.42–1.77	902	92.8	679	71.3	2.85	2.08–3.91	2.86	2.01–4.07	
Missing		6	3						3		1						
Alcohol Use Status																	
Never	14.7	826	1912	25.8	1		1		62	8.0	231	31.2	1		1		<0.0001
Former	26.9	1513	1699	22.9	1.55	1.40–1.72	1.58	1.40–1.79	246	31.9	208	28.1	2.95	2.03–4.29	3.26	2.14–4.97	
Current	58.5	3296	3808	51.3	1.74	1.53–1.97	1.72	1.49–2.00	463	60.1	302	40.8	2.39	1.62–3.53	2.41	1.55–3.74	
Missing		964	1114						204		212						
Number of Drinks/Day[c]																	
Never	13.7	863	2028	24.5	1		1		70	7.6	273	29.3	1		1		<0.0001
>0 to <1	29.6	1868	3822	46.3	1.13	1.02–1.26	1.13	1.00–1.28	166	18.0	368	39.5	1.39	0.96–2.00	1.49	0.98–2.26	
≥1 to <3	22.1	1392	1427	17.3	2.06	1.81–2.34	2.14	1.83–2.48	203	22.0	155	16.7	3.52	2.31–5.37	3.83	2.37–6.19	
≥3 to <5	12.0	755	433	5.2	3.28	2.76–3.89	3.64	2.98–4.45	117	12.7	51	5.5	4.21	2.44–7.28	4.67	2.51–8.69	
≥5	22.6	1426	553	6.7	4.46	3.80–5.25	5.26	4.36–6.34	368	39.8	84	9.0	7.70	4.92–12.06	7.20	4.37–11.87	
Missing		295	270						51		22						
Amount per Day[d]																	
Never	13.7	863	2028	24.5	1		1		70	7.6	273	29.3	1		1		<0.0001
>0 to ≤3	8.6	544	1330	16.1	1.00	0.87–1.15	1.04	0.88–1.22	42	4.6	144	15.5	0.83	0.50–1.40	0.95	0.53–1.70	
>3 to ≤18	23.6	1489	2718	32.9	1.26	1.12–1.41	1.24	1.09–1.42	148	16.0	244	26.2	1.91	1.30–2.81	1.93	1.24–3.01	
>18	54.1	3408	2187	26.5	2.80	2.49–3.15	2.98	2.60–3.41	664	71.9	270	29.0	5.50	3.80–7.95	5.59	3.69–8.47	
		295	270						51		22						
Alcohol Duration[e]																	
Never	15.2	863	2028	26.7	1				70	9.0	273	34.8	1		1		<0.0001
>0 to <20	10.5	596	1002	13.2	1.35	1.17–1.56	1.39	1.17–1.65	51	6.5	106	13.5	1.34	0.82–2.21	1.54	0.88–2.70	
≥20 to <30	15.0	854	979	12.9	1.80	1.56–2.07	1.81	1.56–2.14	126	16.1	96	12.2	3.24	2.04–5.14	3.14	1.81–5.46	
≥30 to <40	22.7	1294	1410	18.6	1.87	1.65–2.13	1.81	1.56–2.12	206	26.4	112	14.3	3.94	2.54–6.11	4.38	2.66–7.21	

Alcohol Use Characteristic	White								Black								LRT p-value[g]
	%	Cases	Controls	%	Adjusted OR[a]	Adjusted 95% CI	Sensitivity Analysis Adjusted OR[a,f]	Sensitivity Analysis Adjusted 95% CI	Cases	%	Controls	%	Adjusted OR[a]	Adjusted 95% CI	Sensitivity Analysis Adjusted OR[a,r]	Sensitivity Analysis Adjusted 95% CI	
≥40	36.6	2083	2169	28.6	1.78	1.58–2.01	1.91	1.67–2.19	328	42.0	198	25.2	3.27	2.20–4.87	3.30	2.14–5.10	
Missing		909	945						194		168						

[a] Odds ratios adjusted for age, sex, study center, educational level, pack-years of smoking, duration of cigar smoking (years), and duration of pipe smoking (years).

[b] Drinking status with 15.6 mL of ethanol in lifetime

[c] 1 drink = 15.6 mL of ethanol

[d] in mL

[e] in years

[f] Odds ratio and 95% CI calculated after exclusion of all oro-pharyngeal cancer cases

[g] This p-value reflects the LRT between each cigarette smoking characteristic and race within all HNC