Gastroesophageal Reflux Disease and Odds of Head and Neck Squamous Cell Carcinoma in North Carolina

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Objectives/Hypothesis: Exposure to excess gastric acid resulting from gastroesophageal reflux disease, also known as acid reflux or heartburn, might contribute to initiation of head and neck squamous cell carcinoma, particularly laryngeal cancer. Prior epidemiologic studies have reported inconsistent results. We sought to clarify this relationship using an observational study with a larger available sample size and better-characterized exposure information than most prior studies.

Study Design: A population-based case-control study of head and neck cancer in North Carolina with 1,340 newly diagnosed cases and 1,378 controls matched on age, race, and sex.

Methods: We used unconditional logistic regression to examine associations between self-reported heartburn and development of overall head and neck cancer as well as development of cancer at specific tumor sites. Subgroup analysis by smoking and alcoholic drinking status was used to make comparisons with a previous study that used a similar study design.

Results: Overall, an increased odds of head and neck cancer was not associated with either self-reported history of heartburn symptoms (odds ratio = 0.85; 95% confidence interval 0.68, 1.06) or self-reported medical diagnosis of GERD (OR = 0.89; 95% CI 0.71, 1.11). These patterns held for specific tumor sites. For laryngopharyngeal cancer, we did not detect any associations regardless of joint smoking and alcoholic drinking status.

Conclusion: Gastroesophageal reflux does not appear to play a role in development of head and neck cancer.

Key Words: Gastroesophageal reflux disease, head and neck squamous cell carcinoma, self-reported measures, epidemiology, population-based studies.

Level of Evidence: 3b.

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INTRODUCTION

Gastroesophageal reflux disease (GERD), also called acid reflux or heartburn, has been linked to increased risk of multiple complications such as esophageal stricture, coughing, and esophageal ulcers.[1,2] It consists of excess acid from the stomach passing up through the esophagus and into the upper aerodigestive tract. This acid exposure has been associated with carcinogenesis, most notably in relation to the development of Barrett's esophagus and subsequently to esophageal cancer.[3,4]

Thus, it is possible that GERD could contribute to the development of head and neck squamous cell carcinoma (HNSCC).[5,6] More specifically, reflux of gastric acid is known to affect the larynx and cause laryngopharyngeal reflux.[7] A large cohort study found that, when compared to the general population, GERD patients had greater incidence of oropharyngeal and hypopharyngeal cancers.[8] Additionally, cell-line studies have shown that gastric acid is carcinogenic for both laryngeal[9] and hypopharyngeal cells.[9,10] Unlike the esophagus, the larynx lacks protective mechanisms against acid such as mucus, peristalsis, and carbonic anhydrase enzyme.[7] Due to its proximity to the upper esophagus, it has been suggested that the larynx could be at higher risk for GERD-based carcinogenesis compared to the oropharynx or oral cavity.

To further address these questions, we examined the associations between GERD and the development of HNSCC in a large population-based case-control study of HNSCC. Relationships between GERD and both overall HNSCC as well as specific tumor sites within the head and neck were evaluated. We hypothesized that a history of having GERD would be associated with greater odds of developing HNSCC, especially laryngeal cancer.

MATERIALS AND METHODS

Study Population

Subjects were drawn from the Carolina Head and Neck Cancer Epidemiology (CHANCE) study, a population-based case-control study that enrolled 1,368 incident cases of HNSCC aged 20 to 80 in a 46-county region of North Carolina during 2002 to 2006.[11,12] Cases were identified by a rapid-case

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ascertainment system through the North Carolina Central Cancer Registry and by contacting cancer registrars at 54 hospitals in the 46 counties during the study period. To be eligible as cases, subjects had to have received a diagnosis of first primary invasive squamous cell carcinoma of the larynx (International Classification of Disease for Oncology, 3rd Edition, topography codes C32.0–C32.9) or oral cavity or pharynx (codes C0.00–C14.8). The study enrolled 1,396 controls who were frequency-matched to cases on age, race, and sex using stratified random sampling. Controls were identified through the North Carolina Department of Motor Vehicle records as residents of the study region aged 20 to 80 years old who had never received a diagnosis of HNSCC. The study collected questionnaire data. Due to the sparse numbers, the present analysis excluded 28 cases and 18 controls whose race was not white or black.

The institutional review board at the University of North Carolina at Chapel Hill approved the protocol. All subjects provided informed consent.

Gastroesophageal Reflux Disease Measures

Gastroesophageal reflux disease exposure was assessed via two different questionnaire items administered in-person by a nurse-interviewer within 2 months of diagnosis. The first question, considered a measure of self-reported GERD symptoms, was: "Were you ever bothered by frequent heartburn?" The second question, considered a measure of medical diagnosis, was: "Did your doctor ever tell you that you had GERD?" Both items were answered "yes," "no," "refused," "don't know," or were recorded as missing. For purposes of analysis, we recoded responses of "refused" or "don't know" as missing.

Covariates

Variables that were considered to be common causes of GERD and HNSCC incidence were selected a priori to include as confounders in multivariable models. All covariates were measured at baseline interview. These included age (categorized as 20–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–80), sex, race (white or black), years smoked cigarettes (never smoker, 1–19 years, 20–39 years, 40–49 years, and 50+ years), lifetime alcohol consumption as described previously (never had alcohol; <11,232 mL; 11,232-<204,469 mL; 204,469-<927,946 mL; 927,946+ mL),[12] body mass index (< 18.5, 18.5– < 25.0, 25.0– < 30.0, and 30.0+), and education (less than high school, high school graduate/vocational training/technical training, and at least some college).

To assign alcohol consumption status for the subgroup analysis by joint alcohol consumption and smoking history status, alcohol consumption was measured in terms of 12-ounce beers, 5-ounce wines, and 1.5-ounce hard liquors per week to more closely approximate the definition of Langevin et al.[6]

Outcomes

Case-control status was the outcome variable. Some analyses examined the associations with overall case-control status (any HNSCC case vs. controls), whereas others examined the associations with specific HNSCC tumor sites (laryngeal, hypopharyngeal, oropharyngeal, or oral cavity) compared to controls. Further analyses combined hypopharyngeal and oropharyngeal cases into overall pharyngeal cases and compared them to controls. Subgroup analyses by joint alcohol consumption and smoking status compared combined laryngeal and pharyngeal cases (i.e., laryngopharyngeal cases) to controls.

The CHANCE enrolled 251 cases designated as not otherwise specified (NOS), that is, those whose tumors could not be assigned to a particular tumor site. Of these, 247 cases were eligible for inclusion in the present analysis. We included NOS cases in the overall case-control status variable but excluded them from tumor site-specific analyses.

Statistical Analysis

Distributions of all variables included in statistical models were computed as frequencies and percentages for overall cases, tumor site-specific cases, and controls. The covariate distributions of overall HNSCC cases and controls were compared using chi-square tests.

To evaluate associations between GERD and overall case-control status, we used standard unconditional logistic regression for a dichotomous outcome to estimate odds ratios (OR) and 95% confidence interval (CI). For analyses of relationships between GERD and specific tumor sites, we used polytomous logistic regression to compare each of laryngeal, hypopharyngeal, oropharyngeal, overall pharyngeal, or oral cavity cases, respectively, to controls. Different multilevel tumor site variables were constructed to include, on the one hand, hypopharyngeal and oropharyngeal cases as separate categories, and on the other hand, overall pharyngeal cases.

To allow comparison with the study by Langevin et al.,[6] we conducted an analysis of GERD with joint stratification by alcohol consumption and smoking history comparing laryngeal and pharyngeal cases combined to controls. Similar to the Langevin study, heavy drinkers were defined as those consuming more than 14 alcoholic drinks per week. One alcoholic drink was defined as, equivalently, 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of hard liquor. Also per Langevin et al., heavy smokers were defined as subjects with more than 18.3 pack-years of cigarette use.

Every model adjusted for all of the confounders described above. In addition, to account for the CHANCE frequency matching, each model adjusted for 2-way and 3-way interaction terms between the matching factors of age, sex, and race. Each model excluded subjects with incomplete information.

P values less than 0.05 were considered statistically significant. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

The study population included 1,340 head and neck cancer cases and 1,378 controls. The site distribution for cases was as follows: 473 larynx, 361 oropharynx, 192 oral cavity, 67 hypopharynx, and 247 not-otherwise-specified site. Table I presents descriptive statistics for subject characteristics. Relative to controls, HNSCC cases smoked for a greater number of years, had greater lifetime alcohol consumption, and were less likely to have attended college. In this univariate analysis, we found no differences between cases and controls in terms of whether they self-reported having had GERD symptoms or received a medical diagnosis of GERD.

Using multivariable modeling, we found no associations between self-reported history of GERD symptoms and case-control status, either for overall case-control status or for specific tumor sites (Table II). Most of the ORs showed that cases had moderately decreased odds of exposure compared to controls. The OR for hypopharyngeal cancer showed an almost 50% increase in odds.

TABLE I.
Subject Characteristics.

Variable	Controls (N = 1,378)	All Cases (N = 1,340)	*P* Value*	Hypopharynx Cases (N = 67)	Larynx Cases (N = 473)	NOS Cases (N = 247)	Oral Cavity Cases (N = 192)	Oropharynx Cases (N = 361)
Age (years)			< 0.0001					
20–49	156 (11%)	254 (19%)		9 (13%)	64 (14%)	58 (23%)	37 (19%)	86 (24%)
50–54	161 (12%)	210 (16%)		16 (24%)	50 (11%)	40 (16%)	20 (10%)	84 (23%)
55–59	207 (15%)	222 (17%)		13 (19%)	71 (15%)	38 (15%)	31 (16%)	69 (19%)
60–64	205 (15%)	229 (17%)		10 (15%)	95 (20%)	41 (17%)	30 (16%)	53 (15%)
65–69	247 (18%)	178 (13%)		7 (10%)	81 (17%)	30 (12%)	25 (13%)	35 (10%)
70–74	231 (17%)	152 (11%)		3 (4%)	73 (15%)	22 (9%)	29 (15%)	25 (7%)
75–80	171 (12%)	95 (7%)		9 (13%)	39 (8%)	18 (7%)	20 (10%)	9 (2%)
Sex			0.0001					
Male	960 (70%)	1,021 (76%)		56 (84%)	372 (79%)	171 (69%)	123 (64%)	299 (83%)
Female	418 (30%)	319 (24%)		11 (16%)	101 (21%)	76 (31%)	69 (36%)	62 (17%)
Race			< 0.0001					
White	1,114 (81%)	989 (74%)		39 (58%)	345 (73%)	188 (76%)	140 (73%)	277 (77%)
Black	264 (19%)	351 (26%)		28 (42%)	128 (27%)	59 (24%)	52 (27%)	84 (23%)
Years Smoked Cigarettes			< 0.0001					
Never smoker	525 (38%)	173 (13%)		5 (8%)	19 (4%)	57 (23%)	21 (11%)	71 (20%)
1–19	293 (21%)	118 (9%)		3 (5%)	26 (6%)	30 (12%)	12 (6%)	47 (13%)
20–39	334 (24%)	499 (38%)		26 (41%)	180 (38%)	68 (28%)	79 (42%)	146 (41%)
40–49	142 (10%)	344 (26%)		19 (30%)	150 (32%)	65 (27%)	47 (25%)	63 (18%)
50+	78 (6%)	194 (15%)		10 (16%)	97 (21%)	25 (10%)	31 (16%)	31 (9%)
Lifetime Alcohol Consumption (mL)			< 0.0001					
Never had alcohol	296 (22%)	125 (10%)		1 (2%)	45 (10%)	27 (12%)	23 (13%)	29 (9%)
<11,232	161 (12%)	58 (5%)		3 (5%)	21 (5%)	15 (7%)	6 (3%)	13 (4%)
11,232-<204,469	406 (31%)	234 (19%)		3 (5%)	77 (18%)	46 (20%)	23 (13%)	85 (25%)
204,469-<927,946	321 (24%)	319 (26%)		12 (20%)	122 (28%)	53 (23%)	42 (23%)	90 (27%)
927,946+	144 (11%)	497 (40%)		40 (68%)	169 (39%)	85 (38%)	86 (48%)	117 (35%)
Body Mass Index			<0.0001					
Underweight (<18.5)	30 (2%)	100 (7%)		14 (21%)	25 (5%)	20 (8%)	20 (10%)	21 (6%)
Normal (18.5- <25.0)	405 (29%)	482 (36%)		26 (39%)	161 (34%)	93 (38%)	88 (46%)	114 (32%)
Overweight (25.0- <30.0)	551 (40%)	434 (32%)		19 (28%)	159 (34%)	71 (29%)	55 (29%)	130 (36%)
Obese (30.0+)	392 (28%)	324 (24%)		8 (12%)	128 (27%)	63 (26%)	29 (15%)	96 (27%)
Education			< 0.0001					
Less than high school	217 (16%)	458 (34%)		32 (48%)	197 (42%)	64 (26%)	67 (35%)	98 (27%)
High school/vocational/tech	490 (36%)	492 (37%)		18 (27%)	173 (37%)	89 (36%)	73 (38%)	139 (39%)
At least some college	671 (49%)	390 (29%)		17 (25%)	103 (22%)	94 (38%)	52 (27%)	124 (34%)
Ever had frequent heartburn			0.8					
No	1,007 (76%)	989 (77%)		43 (69%)	344 (75%)	194 (81%)	145 (81%)	263 (74%)
Yes	315 (24%)	303 (23%)		19 (31%)	112 (25%)	47 (20%)	34 (19%)	91 (26%)
Ever diagnosed with GERD			0.1					
No	994 (77%)	1,008 (79%)		53 (84%)	329 (73%)	200 (84%)	147 (83%)	279 (80%)
Yes	303 (23%)	266 (21%)		10 (16%)	120 (27%)	37 (16%)	31 (17%)	68 (20%)

*Chi-square comparisons between controls and overall cases.
NOS = Not otherwise specified, GERD = gastroesophageal reflux disease

We also found no association between self-reported medical diagnosis of GERD and the odds of overall HNSCC (Table II). Most ORs were again in an inverse direction, but laryngeal cases had a slightly greater odds of having been diagnosed with GERD compared to controls.

In analyses of combined laryngeal and pharyngeal cases, among those who were neither heavy smokers nor heavy drinkers we detected no association between GERD and the development of laryngopharyngeal cancer for either self-reported history of GERD symptoms or medical diagnosis of GERD (Table III). Likewise, no associations between GERD and laryngopharyngeal cancer were detected among subjects who were heavy smokers and/or heavy drinkers (Table III).

TABLE II.
Effects of Self-Reported Heartburn Symptoms and Medical Diagnosis of Gastroesophageal Reflux Disease on Odds of Developing Overall or Tumor Site-Specific Head and Neck Squamous Cell Carcinoma.

	Self-Reported History of Frequent Heartburn*				GERD Diagnosis*			
Cases	Exposed Cases (%)†	Exposed Controls (%)†	OR‡	95% CI	Exposed Cases (%)†	Exposed Controls (%)†	OR‡	95% CI
Overall	303 (23%)	315 (24%)	0.85	0.68, 1.06	266 (21%)	303 (23%)	0.89	0.71, 1.11
Hypopharynx	19 (31%)	315 (24%)	1.49	0.80, 2.79	10 (16%)	303 (23%)	0.74	0.34, 1.64
Larynx	112 (25%)	315 (24%)	0.88	0.65, 1.19	120 (27%)	303 (23%)	1.27	0.94, 1.70
Oral cavity	34 (19%)	315 (24%)	0.72	0.46, 1.11	31 (17%)	303 (23%)	0.85	0.54, 1.32
Oropharynx	91 (26%)	315 (24%)	0.92	0.68, 1.26	68 (20%)	303 (23%)	0.84	0.61, 1.18
Pharynx	110 (26%)	315 (24%)	0.99	0.73, 1.32	78 (19%)	303 (23%)	0.83	0.60, 1.14

*Recorded as dichotomous ever/never.
†Percentages exclude subjects with missing data.
‡Reference group is controls. Estimates adjusted for age, sex, race, years smoked cigarettes, lifetime alcohol consumption, body mass index, education, and 2-way and 3-way interaction terms between age/sex/race.
CI = confidence interval, GERD = gastroesophageal reflux disease, OR = odds ratio.

DISCUSSION

We assessed associations between GERD exposure and the odds of developing HNSCC in a large, population-based case-control study for both overall HNSCC and specific head and neck tumor sites. We did not detect any strong positive associations between GERD and either development of overall HNSCC or development of cancer at any particular head and neck tumor site.

Although none of our associations was statistically significant, the magnitude of some of the point estimates was notable. The point estimate for the association between self-reported history of GERD symptoms and overall HNSCC was 0.85, and the point estimates for most specific tumor sites were clustered near to that value. However, the point estimate for hypopharyngeal cancer was elevated (1.49), suggesting that GERD could be associated with a greater odds of developing hypopharyngeal cancer relative to the other tumor sites that were examined.

When the exposure was medical diagnosis of GERD rather than self-reported history of GERD symptoms, the point estimate for the association of diagnosed GERD with overall HNSCC (0.89) was close to what it had been for self-reported history of GERD symptoms. Again, most of the point estimates for specific tumor sites were clustered around the null value. There were exceptions, however, with laryngeal cancer having an OR of 1.27 and hypopharyngeal cancer having an OR of 0.74.

Our findings for subgroup analyses by joint alcohol consumption and smoking status were not consistent with previous research. A study of 631 cases of laryngopharyngeal cancer conducted in the Boston area with a similar design to our North Carolina study found that, among subjects who were neither heavy drinkers nor heavy smokers, reporting a history of frequent heartburn was associated with a greater odds of developing laryngopharyngeal cancer (OR = 1.78; 95% CI 1.00, 3.16).[6] In our analysis, no association between heartburn and laryngopharyngeal cancer was found despite using similar definitions of heavy drinking and heavy smoking. Among subjects who were heavy drinkers and/or heavy smokers, both studies found no association between heartburn and the development of laryngopharyngeal cancer.

TABLE III.
Odds of Laryngopharyngeal Cancer Associated With Self-Reported History of Heartburn and Formal Diagnosis of GERD Stratified by Heavy Smoking and/or Heavy Drinking Status.

	Self-Reported History of Heartburn*				GERD Diagnosis*			
Subjects	Cases	Controls	OR§	95% CI	Cases	Controls	OR§	95% CI
Neither a heavy smoker nor a heavy drinker†,‡								
Never had heartburn/GERD	103	543	1.00	–	107	541	1.00	–
Ever had heartburn/GERD	26	152	0.91	0.54, 1.54	23	146	0.87	0.51, 1.48
Heavy smoker and/or heavy drinker†,‡								
Never had heartburn/GERD	497	424	1.00	–	501	416	1.00	–
Ever had heartburn/GERD	175	149	0.96	0.72, 1.28	158	142	1.05	0.79, 1.41

*Recorded as dichotomous ever/never.
†Heavy smoking was defined as more than 18.3 pack-years.
‡Heavy drinking was defined as consumption of more than 14 alcoholic drinks per week.
§Estimates adjusted for age, sex, race, years smoked cigarettes, lifetime alcohol consumption, body mass index, education, and 2-way and 3-way interaction terms between age/sex/race.
CI = confidence interval, GERD = gastroesophageal reflux disease, OR = odds ratio.

Likewise, other prior research has reported conflicting results. A European case-control study of 1,774 HNSCC cases found no association between heartburn and specific HNSCC tumor sites, except for an inverse association with hypopharyngeal cancer (OR = 0.64; 95% CI 0.44, 0.93).[13] Another epidemiologic study (1,303 cases) reported that ever-smoker/ever-drinker HNSCC subjects were not more likely to have had a history of GERD than never-smoker/never-drinker HNSCC patients.[14] A small case-control study (120 cases) examined associations between *H. pylori* infection, a cause of GERD, and odds of laryngopharyngeal cancer but found no association (OR = 1.53; 95% CI 0.69, 3.41).[15]

Studies of the etiologic role of GERD in laryngeal cancer have arrived at different conclusions. A meta-analysis concluded that GERD was associated with an increased odds of laryngeal cancer (OR = 2.21; 95% CI 1.53, 3.19) but not pharyngeal cancer, although the pharynx OR was extremely imprecise.[16] A literature review that was not a meta-analysis could not conclude that GERD caused laryngeal cancer, but noted that confounding by alcohol and tobacco consumption were inadequately controlled.[17] A large case-control study conducted in the Veterans Health Administration system (14,449 cases) found no association between GERD and laryngeal cancer (OR = 1.01; 95% CI 0.92, 1.12).[18]

An important strength of our study was examination of two different measures of GERD exposure: 1) self-reported history of symptoms and medical diagnosis and 2) development of HNSCC. A medical diagnosis of GERD is more likely to indicate substantial GERD morbidity than a self-reported history of having had frequent heartburn, resulting in less misclassification. Second, our analysis was based on a large, population-based case-control study, making it representative of a well-defined source population and increasing the precision of the effect estimates. Third, CHANCE has detailed information on alcohol and tobacco consumption, important causes of HNSCC not well measured in a number of previous studies that examined relationships between GERD and HNSCC.[17] This enabled us to appropriately control for the effects of tobacco and alcohol.

In terms of limitations, our assessment of GERD by self-report was not as accurate as an objective measurement such as pH monitoring would be,[5] even when the self-reported measure was medical diagnosis of GERD rather than self-assessment of GERD symptoms. Medical diagnosis of GERD was ascertained by asking subjects whether they were ever diagnosed with GERD by a doctor rather than abstracting the information from medical records. Furthermore, even among self-reported measures of GERD, our simple one-question assessment might not be as accurate or reliable as validated multi-question instruments such as the Reflux Symptom Index.[19] However, alternative measures of self-reported GERD were not available in CHANCE. There is the possibility of misclassification of the history of GERD, especially if subjects are not aware of the criteria for frequency and severity of symptoms used to diagnose GERD.[20] For example, subjects who are not aware of frequency criteria and assume that their symptoms do not occur frequently enough to warrant being considered a medical diagnosis could falsely report not having had GERD exposure, thereby possibly attenuating estimates of an association between GERD and HNSCC.

Future research on GERD and HNSCC must consider the differing study designs and inconsistent findings of results reported to date. A larger study may be beneficial to further elucidate this association. Such a study would need to provide adequate control for tobacco and alcohol consumption as well as obesity, as was done here.[5] It would be informative to compare the effect of GERD when measured by self-report, medical diagnosis as ascertained by medical records, and by pH monitoring or another objective measurement. Multiple measures of self-reported GERD could be used for purposes of comparison, including questionnaires such as the Reflux Symptom Index.[19] Because a few of our site-specific associations suggested greater risk, estimates of the association of GERD with HNSCC should be conducted for both overall HNSCC as well as individual tumor sites, as was done here.

CONCLUSION

In summary, we find no general pattern of association between GERD and the development of HNSCC. Subgroup analysis of subjects who were neither heavy drinkers nor heavy smokers does not show an association between GERD and the development of laryngopharyngeal cancer, a finding that conflicts with prior research. However, whereas none of our associations is statistically significant, the patterns of some point estimates, such as the larynx result, are suggestive and should be further investigated in future larger studies. Such additional work would help to resolve the inconsistencies observed in this literature.

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