Research Article

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Gastric Reflux Is an Independent Risk Factor for Laryngopharyngeal Carcinoma

Scott M. Langevin[1,2], Dominique S. Michaud[1], Carmen J. Marsit[4,5], Heather H. Nelson[6,7], Ariel E. Birnbaum[3], Melissa Eliot[1], Brock C. Christensen[4,5], Michael D. McClean[8], and Karl T. Kelsey[1,2]

Abstract

Background: Gastric reflux can reach into the upper airway, inducing cellular damage in the epithelial lining. This condition is believed to be a risk factor for development of laryngopharyngeal squamous cell carcinoma (LPSCC), although the literature is conflicting.

Methods: To better clarify this relationship, we assessed the association of self-reported heartburn history and medication use among 631 patients with LPSCCs and 1234 control subjects (frequency-matched on age, gender, and town of residence) enrolled as part of a population-based case–control study of head and neck squamous cell carcinoma in the greater Boston area.

Results: After adjusting for age, gender, race, smoking, alcohol consumption, HPV16 seropositivity, education, and body mass index, subjects reporting a history of frequent heartburn and who were neither a heavy smoker nor heavy drinker had a significantly elevated risk of LPSCCs [OR, 1.78; 95% confidence interval (CI), 1.00–3.16]. Among those with a history of heartburn, there was an inverse association between antacid use and LPSCCs relative to those never taking heartburn medication (OR, 0.59; 95% CI, 0.38–0.93) that remained consistent when analyzed by smoking/drinking status, HPV16 status, or by primary tumor site.

Conclusions: Our data show that gastric reflux is an independent risk factor for squamous cancers of the pharynx and larynx. Further studies are needed to clarify the possible chemopreventive role of antacid use for patients with gastric reflux.

Impact: Elucidation of additional risk factors for head and neck cancer can allow for risk stratification and inform surveillance of high-risk patients. *Cancer Epidemiol Biomarkers Prev; 22(6); 1061–8. ©2013 AACR.*

Introduction

It is estimated that head and neck cancer will account for approximately 52,610 new cancer cases and 11,500 deaths in the United States in 2012 (1). Malignancies originating in the pharynx and larynx, which are predominantly of a squamous histologic origin (LPSCCs), comprise about half of all these cancers. In addition to a relatively high mortality, with a 5-year survival rate around 60% (2), this disease often necessitates debilitating treatments that result in high morbidity, particularly inhibition of basic functions such as speech, swallowing, and breathing (3). While smoking, alcohol consumption, and HPV16 infection constitute the major risk factors, other factors such as diet (4–9), environmental and occupational exposures (10), dentition and oral hygiene (11–13), gastroesophageal reflux (14–16), and inherited cancer syndromes (17) have also been associated with the disease.

The burning sensation in the upper digestive tract commonly referred to as heartburn is associated with the backflow of gastric acid into the esophagus and is a chief symptom of gastroesophageal reflux disease (GERD; ref. 18). This can occur as a result of several pathophysiologic conditions impacting acid production, gastric pressure, esophageal clearance, or the strength and fit of the lower esophageal sphincter (19). The prevalence of GERD is estimated at 10% to 20% in Western populations (20), with risk factors that include male gender, obesity, smoking, and diet (18, 21). Reflux of gastric acid, a major risk factor for esophageal cancer (22), can reach beyond the esophagus into the laryngopharynx (known as laryngopharyngeal reflux) as shown by 24-hour pH monitoring probes (23–26). Although reflux has primarily been implicated in esophageal adenocarcinoma, esophageal squamous epithelium typically undergoes intestinal metaplasia in response to chronic exposure to gastric acid, which in turn develops into adenocarcinoma (27), whereas such a metaplastic transformation is not commonplace in the pharynx or larynx. It has been hypothesized that

Authors' Affiliations: Departments of [1]Epidemiology, [2]Pathology and Laboratory Medicine, and [3]Medicine, Brown University, Providence, Rhode Island; Departments of [4]Pharmacology and Toxicology and [5]Community and Family Medicine, Dartmouth Medical School, Lebanon, New Hampshire; [6]Masonic Cancer Center; [7]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota; and [8]Department of Environmental Health, Boston University School of Public Health, Boston, Massachusetts

Corresponding Author: Karl T. Kelsey, Brown University, 70 Ship Street, Box G-E5, Providence, RI 02912. Phone: 401-863-6420; Fax: 401-863-9008; E-mail: karl_kelsey@brown.edu

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laryngopharyngeal reflux can damage the epithelium of the larynx and pharynx through induction of chronic inflammation (28), production of reactive oxygen and nitrogen species (29), intracellular acidification (29), and activation of proliferative signaling pathways (29–31), all of which can ultimately contribute to malignant transformation. A number of studies have investigated the association between heartburn or GERD and risk for laryngeal and/or pharyngeal cancer (14, 23, 24, 32–38), with mixed results.

Elucidation of additional risk factors for head and neck cancer can allow for risk stratification and inform surveillance of high-risk patients. As gastric reflux can reach into the larynx and pharynx, the goal of this study is to evaluate the relationship between LPSCCs and history and severity of heartburn to provide better clarity about its role as a risk factor for the disease and to explore the use of heartburn medication regimens for LPSCC prevention. Novel aspects of our study include evaluation of medication use on LPSCC risk among patients reporting heartburn and the assessment of effect modification of heartburn history and medication use by smoking/drinking or HPV16 exposure.

Materials and Methods

Study population

Incident cases of head and neck squamous cell carcinoma (HNSCC) were enrolled through major teaching hospitals located in Boston, MA (Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Boston Medical Center, Dana-Farber Cancer Institute, Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, and New England Medical Center) as part of a population-based case–control study of the greater Boston area (39, 40). There were 646 cases of LPSCCs available through the study: 476 pharyngeal and 170 laryngeal cancers. Control subjects ($n = 1{,}252$) with no prior history of head and neck cancer were selected using town records and frequency-matched to HNSCC cases on age (± 3 years), gender, and neighborhood/town of residence. The study includes data collected from 2 periods of recruitment from the same population: phase I was conducted between December 1999 and December 2003 (285 LPSCC cases and 685 controls) and phase II was conducted between October 2006 and June 2011 (361 LPSCC cases and 567 controls). Participation rates for cases and controls were 78% and 47%, respectively. Subjects who did not report any reflux data were excluded (15 cases and 18 controls), leaving 631 cases and 1,234 controls for analysis; of these, heartburn medication history was available for 627 cases (99.4%) and 1,228 controls (99.5%) and heartburn frequency (never, rare, often) was available for 524 cases (83.0%) and 925 controls (75.0%). All cases and controls enrolled in the study provided written informed consent as approved by the Institutional Review Boards of the participating institutions.

Data collection

Subjects completed a self-administered epidemiologic questionnaire that provided detailed data on sociodemographics and personal characteristics, alcohol and tobacco use, personal and family cancer history, history of heartburn and other relevant dietary, occupational, residential, and medical exposures.

HPV serology

Serologic HPV16 testing for L1 viral protein antibody was conducted on all cases and controls as a measure of past exposure to HPV16. Sandwich ELISA assays were used for detection of HPV16 antibodies as previously described (41).

Statistical analysis

Descriptive statistics were generated according to case–control status and by primary tumor site. Normality of continuous covariates was evaluated using the skewness–kurtosis test (42). Two-sample t tests were used to assess differences between normally distributed continuous variables. Fisher's exact test was used to assess differences between categorical variables. All tests were 2-sided and significance was considered where $P \leq 0.05$.

Unconditional multivariable logistic regression was used to examine the association between heartburn frequency and medication history, respectively, and LPSCCs, overall and by primary tumor site (i.e., pharynx or larynx). For the purpose of the site-specific analyses, oropharyngeal and hypopharyngeal cases were considered together, as only 18 of the 468 pharyngeal cases originated in the hypopharynx (4%). Heartburn frequency was categorized on the basis of self-reported data as *never*, *rare*, and *often/extreme*. Heartburn medication history among those reporting ever having experienced heartburn was categorized as *never took medicine*, *antacids only*, *ever-use of proton pump inhibitors (PPI)*, and/or *histamine H2 receptor antagonists* (2 major classes of heartburn treatment drugs used to reduce gastric acid production), and *other medications/home remedies*. All models were adjusted for age (continuous, centered at the mean), gender, race (*White* or *non-White*), smoking, alcohol consumption, HPV16 exposure (*positive* or *negative* for L1 antibodies), education (*high school or less* or *beyond high school*), and body mass index (BMI). BMI was modeled categorically according to World Health Organization guidelines for adult BMI classification (43): *underweight* (BMI < 18.5), *normal* ($18.5 \leq$ BMI < 25), *overweight* ($25 \leq$ BMI < 30), and *obese* (BMI ≥ 30). Smoking was categorized as *never-smoker* or by tertile of pack-years (calculated as the average number of cigarette packs smoked per day multiplied by total years of smoking) for ever-smokers (*I tertile*: 0.1–18.3 pack-years; *II tertile*: 18.4–41.0 pack-years; *III tertile*: 41.1–202.5 pack-years). Alcohol consumption was categorized as *non-drinker*, *≤14 drinks per week*, and *>14 drinks per week* based on a typical week during adult life, where one drink was considered to be consumption of 12 oz of beer, 5 oz of wine, or 1.5 oz of liquor. Covariate data were missing for

race (1 case, 1 control), alcohol consumption (1 case, 2 controls), education (1 case, 8 controls), BMI (77 cases, 22 controls), and HPV16 serology (77 cases, 175 controls). Dummy variables for missing BMI and HPV16 serology data were generated and included in the models; the remaining 14 subjects (3 cases, 11 controls) missing race, alcohol, or education data were excluded from the multivariable analyses. As a sensitivity analysis to explore the introduction of bias through use of dummy coding to account for missing BMI and HPV16 serology data, the aforedescribed models were reanalyzed, excluding all subjects with missing covariate data.

Models were additionally stratified by heavy smoking/drinking status (*heavy smoker and/or heavy drinker* vs. *neither a heavy smoker nor heavy drinker*), where heavy smokers were defined as subjects smoking more than 18.3 total pack-years (≥II tertile of control smokers) and heavy drinkers were defined as those consuming more than 14 alcoholic beverages per week; and HPV16 serostatus (*positive* vs. *negative*) based on antibodies to the L1 viral protein. Stratified models were conducted for LPSCCs (but not by primary tumor site due to sample size/power limitations). Interactions between heartburn history or medication use and each stratifying variable were tested by including a multiplicative term between the respective covariates in the model and were considered significant where $P \leq 0.10$.

All statistical analyses were conducted using Stata 11.

Results

A description of the demographic, health behavior, and tumor characteristics of the study population by case–control status and primary tumor site is provided in Table 1. Cases were significantly older than controls ($P = 0.01$),

Table 1. Description of the study population by case–control status and primary tumor site

				LPSCC by Primary Site		
	Controls ($N = 1,234$)	LPSCC ($N = 631$)	$P_{difference}$	Pharyngeal ($N = 468$)	Laryngeal ($N = 163$)	$P_{difference}$
Age, mean y (σ)	60.9 (11.1)	59.5 (10.4)	0.01[a]	58.9 (10.4)	61.1 (10.4)	0.02[c]
Gender, *n* (%)						
Female	333 (27.0%)	132 (20.9%)	0.01[b]	91 (19.4%)	41 (25.2%)	0.15[d]
Male	901 (73.0%)	499 (79.1%)		377 (80.6%)	122 (74.9%)	
Race, *n* (%)						
White	1114 (90.4%)	572 (90.8%)	0.80[b]	427 (91.4%)	145 (89.0%)	0.35[d]
Non-White	119 (9.7%)	58 (9.2%)		40 (8.6%)	18 (11.0%)	
Cigarette smoking, *n* (%)						
Never-smoker	497 (40.3%)	144 (22.8%)	<0.001[b]	123 (26.3%)	21 (12.9%)	<0.001[d]
I tertile (0.1–18.3 pack-years)	282 (22.9%)	143 (22.7%)		118 (25.2%)	25 (15.3%)	
II tertile (18.4–41.0 pack-years)	254 (20.6%)	161 (25.5%)		114 (24.4%)	47 (28.8%)	
III tertile (41.1–202.5 pack-years)	201 (16.3%)	183 (29.0%)		113 (24.2%)	70 (42.9%)	
Alcohol consumption, *n* (%)						
Non-drinker	151 (12.3%)	51 (8.1%)	<0.001[b]	34 (7.3%)	17 (10.4%)	0.01[d]
≤14 drinks/wk	787 (63.9%)	282 (44.8%)		226 (48.4%)	56 (34.4%)	
>14 drinks/wk	294 (23.9%)	297 (47.1%)		207 (44.3%)	90 (55.2%)	
BMI, *n* (%)						
Underweight (BMI < 18.5)	17 (1.4%)	29 (4.9%)	<0.001[b]	20 (4.5%)	9 (6.0%)	0.66[d]
Normal (18.5 ≤ BMI < 25)	337 (27.9%)	276 (46.7%)		210 (47.5%)	66 (44.3%)	
Overweight (25 ≤ BMI < 30)	468 (38.7%)	207 (35.0%)		156 (35.3%)	51 (34.2%)	
Obese (BMI ≤ 30)	387 (32.0%)	79 (13.4%)		56 (12.7%)	23 (15.4%)	
Highest level of education, *n* (%)						
High school or less	340 (27.7%)	249 (39.5%)	<0.001[b]	167 (35.7%)	82 (50.6%)	0.001[d]
Beyond high school	886 (72.3%)	381 (60.5%)		301 (64.3%)	80 (49.4%)	
HPV16 serology (L1), *n* (%)						
Negative	993 (93.7%)	336 (60.7%)	<0.001[b]	221 (53.3%)	115 (82.7%)	<0.001[d]
Positive	67 (6.3%)	218 (39.4%)		194 (46.8%)	24 (17.3%)	

Abbreviation: σ, SD.

[a]*t* test for difference between cases (all LPSCC) and controls.

[b]Fisher's exact test for difference between cases (all LPSCC) and controls.

[c]*t* test for difference across primary tumor sites (cases only).

[d]Fisher's exact test for difference across primary tumor sites (cases only).

Table 2. Heartburn medication history by heartburn frequency and case–control status

	Study subjects having ever experienced heartburn[a]					
	All LPSCC			Controls		
Heartburn medication history[b]	Rare	Often	$P_{difference}$[c]	Rare	Often	$P_{difference}$[d]
None	91 (42.7%)	8 (7.2%)	<0.001	155 (41.2%)	7 (4.0%)	<0.001
Antacids only	63 (29.6%)	14 (12.6%)		147 (39.1%)	36 (20.7%)	
PPI or H2 receptor antagonists	50 (23.5%)	83 (74.8%)		52 (13.8%)	118 (67.8%)	
Also used antacids	18 (8.5%)	21 (18.9%)		18 (4.8%)	35 (20.1%)	
Never used antacids	32 (15.0%)	62 (55.9%)		34 (9.0%)	83 (47.7%)	
Other medications or home remedies	9 (4.2%)	6 (5.4%)		22 (5.9%)	13 (7.5%)	

Abbreviation: PPI, proton pump inhibitor.

[a]Subjects with available heartburn medication data but who did not supply heartburn frequency data were excluded from this table.

[b]Medication data were missing for a total of 5 cases (4 rare, 1 often/extreme) and 5 controls (3 rare, 2 often/extreme) with available heartburn frequency data.

[c]Fisher's exact test for difference across medication use categories by heartburn frequency among LPSCC cases.

[d]Fisher's exact test for difference across medication use categories by heartburn frequency among controls.

although the median age was only 1.4 years older, and were more likely to be male ($P = 0.01$). Relative to controls, cases smoked more ($P < 0.001$), were more likely to consume more than 14 alcoholic beverages per week ($P < 0.001$), had a higher prevalence of L1 antibody for HPV16, were more likely to have a BMI in normal range and less likely to be obese ($P < 0.001$), and were less educated ($P < 0.001$). Pharyngeal cases were an average of 2.2 years older than laryngeal cases ($P = 0.02$). Pharyngeal and laryngeal cases also significantly differed by smoking ($P < 0.001$), alcohol consumption ($P = 0.01$), education ($P = 0.001$), and HPV16 serology ($P < 0.001$).

There were significant differences in usage of most types of heartburn medication by heartburn frequency (Table 2). As expected, study subjects reporting often/extreme occurrence of heartburn were much more likely to report use of PPI or histamine H2 receptor antagonists than those reporting only rare occurrence of heartburn.

Table 3. Association of self-reported heartburn frequency and medication history with laryngopharyngeal carcinoma, overall and by primary tumor site

	All LPSCC		Pharyngeal		Laryngeal	
	$n_{cases}/n_{control}$	OR[a] (95% CI)	$n_{cases}/n_{control}$	OR[a] (95% CI)	$n_{cases}/n_{control}$	OR[a] (95% CI)
Heartburn frequency[b]						
Never had heartburn	195/366	Reference	147/366	Reference	48/366	Reference
Rare	217/379	1.01 (0.75–1.36)	171/379	1.03 (0.74–1.44)	46/379	0.83 (0.51–1.34)
Often/extreme	110/172	1.16 (0.80–1.68)	88/172	1.23 (0.82–1.85)	22/172	0.84 (0.45–1.55)
Heartburn medication history[c,d]						
Never took medicine	126/241	Reference	91/241	Reference	35/241	Reference
Antacids only	116/312	**0.59 (0.38–0.93)**	87/312	0.71 (0.43–1.16)	29/312	**0.33 (0.14–0.79)**
PPI and/or histamine H2 receptor antagonist	167/242	1.38 (0.85–2.26)	121/242	1.34 (0.77–2.34)	46/242	1.97 (0.88–4.78)
Other medications/home remedies	20/56	0.94 (0.42–2.09)	17/56	1.41 (0.61–3.26)	3/56	—

NOTE: Significant results are shown in bold type.

Abbreviation: PPI, proton pump inhibitor.

[a]Adjusted for age, sex, race, smoking, alcohol consumption, HPV16 exposure (L1 serology), education, and BMI.

[b]Two cases (1 pharyngeal, 1 laryngeal) and 8 controls were excluded from the models due to missing data for race, alcohol consumption, or education.

[c]Restricted to subjects reporting ever having heartburn; 2 cases (1 pharyngeal, 1 laryngeal) and 8 controls were excluded due to missing data for race, alcohol consumption, or education.

[d]Additionally adjusted for heartburn frequency.

Table 4. Self-reported heartburn frequency, medication history, and laryngopharyngeal carcinoma risk stratified by heavy smoking and/or heavy drinking status

	$n_{cases}/n_{control}$	OR[a] (95% CI)	
Heartburn frequency			
Neither a heavy smoker[b] nor heavy drinker[c]			
Never had heartburn	66/225	Reference	
Rare	78/199	1.02 (0.64–1.63)	
Often/extreme	39/80	**1.78 (1.00–3.16)**	
Heavy smoker[b] and/or heavy drinker[c]			$P_{interaction} = 0.07$
Never had heartburn	129/141	Reference	
Rare	139/180	0.96 (0.65–1.43)	
Often/extreme	71/92	0.84 (0.52–1.38)	
Heartburn medication history[d–f]			
Neither a heavy smoker[b] nor heavy drinker[c]			
Heartburn—never took medicine	44/129	Reference	
Heartburn—antacids only	29/146	0.60 (0.28–1.27)	
Heartburn—PPI and/or histamine H2 receptor antagonist	60/113	1.21 (0.55–2.63)	
Heavy smoker[b] and/or heavy drinker[c]			$P_{interaction} = 0.92$
Heartburn—never took medicine	82/112	Reference	
Heartburn—antacids only	87/166	0.65 (0.36–1.17)	
Heartburn—PPI and/or histamine H2 receptor antagonist	107/129	1.65 (0.85–3.21)	

NOTE: Significant results are shown in bold type.

Abbreviation: PPI, proton pump inhibitor.

[a]Adjusted for age, sex, race, smoking, alcohol consumption, HPV16 exposure, education, and BMI.

[b]Heavy smoker was defined as the II and III tertiles of pack-years among smokers (>18.3 pack-years).

[c]Heavy drinker was defined as consumption of more than 14 alcoholic drinks per week.

[d]Restricted to subjects reporting ever having heartburn.

[e]Additionally adjusted for heartburn frequency.

[f]Subjects reporting treatment of heartburn solely with other medications or home remedies only were excluded from the analysis due to low frequency of occurrence.

Conversely, subjects reporting rare heartburn were more likely to report not taking medication or taking antacids alone than subjects reporting having often/extreme heartburn occurrence.

No association was observed between frequent heartburn LPSCCs relative to those never experiencing heartburn (overall or by primary tumor site), after adjusting for age, sex, race, smoking, alcohol consumption, HPV16, education, and BMI (Table 3). Among those reporting ever having experienced heartburn, only using antacids for treatment was significantly inversely associated with LPSCCs [OR, 0.59; 95% confidence interval (CI), 0.38–0.93] and laryngeal carcinoma (OR, 0.33; 95% CI, 0.14–0.79); there also was an inverse (although nonsignificant) point estimate for the association with pharyngeal carcinoma (OR, 0.71; 95% CI, 0.43–1.16).

To further assess the independent association of heartburn with LPSCCs, we stratified our analyses by heavy smoking/drinking status (Table 4). A history of frequent heartburn was significantly associated with LPSCCs among subjects who were neither heavy smokers nor heavy drinkers (OR, 1.78; 95% CI, 1.00–3.16). Strengthening this finding, we observed no association when we conducted the same analysis *ad hoc* in squamous cell carcinoma of the oral cavity (OR_{rare}, 1.35; 95% CI, 0.85–2.16; $OR_{often/extreme}$, 1.04; 95% CI, 0.53–2.04), where reflux does not tend to reach. No association was observed between heartburn and LPSCCs among heavy smokers and/or heavy drinkers.

When examining the association between heartburn medication history and LPSCCs by HPV16 serostatus, there was a significant inverse association between antacid use and LPSCCs, relative to those experiencing heartburn but never taking medication for it among subjects who were HPV16 L1 seronegative (OR, 0.50; 95% CI, 0.29–0.85), although no significant effect modification was observed with HPV16 serostatus (Table 5).

Sensitivity analyses in which all models were reanalyzed excluding subjects with dummy coded missing BMI or HPV16 serology data yielded similar estimates (data not shown).

Discussion

We report a significant positive association between a history of frequent heartburn and LPSCCs among people who were neither a heavy smoker nor heavy drinker, strongly supporting prior indications that gastric reflux is an independent risk factor for these malignancies. There

Table 5. Self-reported heartburn frequency, medication history, and laryngopharyngeal carcinoma risk stratified by HPV16 L1 antibody serostatus

	$n_{cases}/n_{control}$	OR[a] (95% CI)	
Heartburn frequency			
HPV16 L1 negative			
Never had heartburn	99/298	Reference	
Rare	116/306	1.14 (0.80–1.62)	
Often/extreme	49/136	1.17 (0.75–1.83)	
HPV16 L1 positive			$P_{interaction} = 0.43$
Never had heartburn	62/19	Reference	
Rare	86/27	0.94 (0.43–2.06)	
Often/extreme	50/7	2.27 (0.79–6.52)	
Heartburn medication history[b–d]			
HPV16 L1 negative			
Heartburn—never took medicine	74/192	Reference	
Heartburn—antacids only	60/251	**0.50 (0.29–0.85)**	
Heartburn—PPI and/or histamine H2 receptor antagonist	88/193	1.59 (0.88–2.87)	
HPV16 L1 positive			$P_{interaction} = 0.29$
Heartburn—never took medicine	41/13	Reference	
Heartburn—antacids only	44/17	0.73 (0.23–2.36)	
Heartburn—PPI and/or histamine H2 receptor antagonist	62/15	0.54 (0.15–1.96)	

NOTE: Significant results are shown in bold type

Abbreviation: PPI, proton pump inhibitor.

[a]Adjusted for age, sex, race, smoking, alcohol consumption, HPV16 exposure, education, and BMI.

[b]Restricted to subjects reporting ever having heartburn.

[c]Additionally adjusted for heartburn frequency.

[d]Subjects reporting treatment of heartburn solely with other medications or home remedies only were excluded from the analysis due to low frequency of occurrence.

was a consistent inverse association between antacid use and LPSCCs among those reporting ever having experienced heartburn, after adjusting for heartburn frequency and other potential confounders.

Our observed association between frequent heartburn history and LPSCCs is consistent with the findings of several published studies on the relationship between gastric reflux and laryngeal and/or pharyngeal cancer, which used a variety of approaches to define reflux, including medical records history of GERD (14, 37), endoscopic findings (32, 35, 38), and 24-hour pH probe monitoring (23, 24). At the same time, the current literature lacks consistency and clarity, as many of these studies were based on small number of cases (23, 24, 26, 32, 36, 38), did not adjust for potential confounding (23, 24, 26, 35, 38), or were cross-sectional in nature (23, 24, 26, 35, 38). However, the 2 case–control studies that examined medical history of GERD based on medical record review did not suffer from these issues and corroborate our findings with estimates in line with our own, with respective OR estimates of 2.31 and 2.11 (14, 37). Furthermore, not all studies reported an association of heartburn history with laryngopharyngeal cancer (26, 34, 36). For instance, one large case–control study of 14,449 patients with laryngeal cancer with 14,449 controls matched on age, gender, and race/ethnicity that used outpatient medical record data from the Veterans Health Administration (34) found no association, although control for confounding was poor, as smoking and alcohol consumption were determined on the basis of administrative data [smoking was classified indirectly based on ICD-9 codes for tobacco use and/or chronic obstructive pulmonary disorder (COPD)].

We also observed an inverse association between antacid use and LPSCCs among subjects with a heartburn history. This does not appear to be a sporadic finding as the observed protective effect was consistent across analyses regardless of smoking or drinking status, HPV16 serology or primary tumor site (including oral cancer). It is possible that the observation is confounded by some unaccounted factor, although this study is well-controlled for known risk factors of LPSCCs. Mechanistically, it is biologically plausible that antacid use confers anticancer protection by neutralizing the pH of the reflux reaching the upper aerodigestive tract, leading to a decrease in inflammation and reducing DNA damage stemming from increased levels of cellular acidity. We also observed an elevated, although nonsignificant, LPSCC risk among those taking proton pump inhibitors or histamine H2 receptor antagonists for heartburn. However, it should be noted that patients taking these medications are likely biased toward those with the most severe reflux and thus these findings may be more a reflection of severity than

medication efficacy. As this is an observational study (and therefore susceptible to certain biases), more research is needed regarding the possible protective effects of antacid use against LPSCCs in patients with gastric reflux.

The strengths of this report include the relatively large sample size of this population-based case–control study; the well-characterized exposures and patient data, including HPV16 serology, enabling thorough control of potential confounding; and collection of detailed data on heartburn medication use. However, there are also several limitations. Because of the retrospective nature of this study and lack of available date ranges for heartburn symptoms and medication use, we cannot fully rule out reverse causality. While it is plausible that heartburn may have resulted from not-yet-diagnosed LPSCCs, our study patients were asked to recall their symptoms before cancer diagnosis, reducing the likelihood that the malignancy is the cause of the reflux. Furthermore, a study by El-Serag and colleagues (14) found the average time from GERD to cancer diagnosis to be 3 to 4 years, suggesting a causal temporal relationship. While we cannot fully rule out the possibility of recall bias due to our use of self-reported data in a retrospective case–control study design, our findings were similar to those of 2 case–control studies of laryngeal and/or pharyngeal cancer that used hospital records to define a GERD diagnosis (14, 37), which would mitigate any potential for differential reporting of reflux between cases and controls in these studies. It is additionally possible that our use of self-reported heartburn does not accurately reflect laryngopharyngeal reflux, which is not always symptomatic. Because of lack of defenses and lower pH in the larynx and pharynx, it takes a much smaller amount of gastric acid to induce damage in the upper airways relative to the esophagus and therefore may not produce heartburn symptoms (44). However, this would likely bias our results toward the null indicating that the actual effect size may be greater than what was observed.

In summary, our findings strongly support gastric reflux as an independent risk factor for LPSCCs, helping to clarify the body of literature on this topic. In addition, we report a consistent inverse association between antacid use and LPSCCs among subjects ever having experienced heartburn symptoms, suggesting the efficacy of this regimen in reducing the risk of LPSCC attributable to gastric reflux. Future studies should aim to replicate this observation with antacid use to determine whether it truly has anticancer chemopreventive properties. Continued efforts at elucidating additional risk factors for head and neck cancer beyond the major known risk factors (i.e., smoking, alcohol consumption, and HPV16) will enhance the ability of clinicians and public health practitioners to identify high-risk patient populations and work towards reducing the morbidity and mortality impact of this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.M. Langevin, H.H. Nelson, K.T. Kelsey
Development of methodology: S.M. Langevin, K.T. Kelsey
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.M. Langevin, M.D. McClean, K.T. Kelsey
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.M. Langevin, D.S. Michaud, C.J. Marsit, H.H. Nelson, M. Eliot, B.C. Christensen, K.T. Kelsey
Writing, review, and/or revision of the manuscript: S.M. Langevin, D.S. Michaud, C.J. Marsit, H.H. Nelson, B.C. Christensen, M.D. McClean, K.T. Kelsey
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Eliot, M.D. McClean, K.T. Kelsey
Study supervision: A.E. Birnbaum, M.D. McClean, K.T. Kelsey

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