Research Article

Cancer Prevention Research

Proton Pump Inhibitors and Histamine 2 Blockers Are Associated with Improved Overall Survival in Patients with Head and Neck Squamous Carcinoma

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Abstract

It has been postulated that gastroesophageal reflux plays a role in the etiology of head and neck squamous cell carcinomas (HNSCC) and contributes to complications after surgery or during radiotherapy. Antacid medications are commonly used in patients with HNSCC for the management of acid reflux; however, their relationship with outcomes has not been well studied. Associations between histamine receptor-2 antagonists (H2RA) and proton pump inhibitors (PPI) use and treatment outcomes were determined in 596 patients with previously untreated HNSCC enrolled in our SPORE epidemiology program from 2003 to 2008 (median follow-up 55 months). Comprehensive clinical information was entered prospectively in our database. Risk strata were created on the basis of possible confounding prognostic variables (age, demographics, socioeconomics, tumor stage, primary site, smoking status, HPV16 status, and treatment modality); correlations within risk strata were analyzed in a multivariable model. Patients taking antacid medications had significantly better overall survival (OS; PPI alone: $P < 0.001$; H2RA alone, $P = 0.0479$; both PPI + H2RA, $P = 0.0133$). Using multivariable Cox models and adjusting for significant prognostic covariates, both PPIs and H2RAs used were significant prognostic factors for OS, but only H2RAs use for recurrence-free survival in HPV16-positive oropharyngeal patients. We found significant associations between the use of H2RAs and PPIs, alone or in combination, and various clinical characteristics. The findings in this large cohort study indicate that routine use of antacid medications may have significant therapeutic benefit in patients with HNSCC. The reasons for this association remain an active area of investigation and could lead to identification of new treatment and prevention approaches with agents that have minimal toxicities. *Cancer Prev Res; 7(12); 1258–69. ©2014 AACR.*

Introduction

Pathologic gastroesophageal reflux is a common condition in patients with head and neck cancer (1–4). There is evidence that acid reflux may play a role in the etiology of head and neck squamous cell cancer (HNSCC) and contribute to complications after surgery or during radiation and chemotherapy (2, 5–9); acid reflux has been recently reported as an independent risk factor for squamous cancers of the pharynx and larynx (10). Histamine receptor-2 antagonists (H2RA) and proton pump inhibitors (PPI) are distinct groups of medications known for their similar ability to decrease and/or inhibit gastric acid production. At the University of Michigan (Ann Arbor, MI), these medications are commonly and regularly administered in patients with HNSCC as part of their cancer treatment for the management of acid reflux and complications from conventional therapies. It is unknown whether preventing acid reflux might prevent tumor recurrences and improve clinical outcome in patients with HNSCC.

The objective of this study was to determine whether clinical use of antacid drugs is associated with better clinical outcomes in a large retrospective cohort of 596 previously untreated patients enrolled in our Head and Neck Cancer Specialized Program of Research Excellence (SPORE) epidemiology program from 2003 to 2008. This is the first study to identify an association of the PPI and H2RA class of drugs with treatment outcomes and survival in patients with HNSCC. Elucidation of antacid drugs biologic effects on

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doi: 10.1158/1940-6207.CAPR-14-0002

tumor progression could lead to new strategies for cancer prevention and treatment.

Materials and Methods

Patient population

Permission from the Institutional Review Board (IRB) for Human studies was granted to retrospectively analyze the patients that presented to the Department of Otolaryngology between January29, 2003 and November 7, 2008 with HNSCC who were enrolled in our prospective Head and Neck SPORE epidemiology program. IRB approval was also granted for use of existing clinical health data regarding medication use from the medical records of the patients. All patients included provided informed and signed consent form.

The initial cohort of 884 unselected subjects prospectively completed longitudinal health surveys which collected health behaviors (tobacco and alcohol usage), quality of life measures, patient demographics (age, gender, race, marital status, US Armed Forces veteran status), and socioeconomic status (education level and median income from Census tract). The clinical and treatment outcome data were collected through SPORE data collection forms and health surveys. The investigators collected clinical and histopathologic information (primary tumor site, TNM stage, HPV16 status for oropharyngeal primaries), and follow-up information (type of treatment, duration of follow-up in months, incidence of recurrences, patterns of relapse, overall, and cause-specific survival). Patient drug use was identified by retrospective chart review and data abstraction from patient electronic health records CareWeb using the University of Michigan's EMERSE (Electronic Medical Record Search Engine) software. Using this custom designed software, we were able to create complex yet precise search queries to identify drugs taken and in which time periods (pre- or post-treatment), baseline demographics, clinical and histopathologic data in this cohort. Data were independently collected by three investigators to minimize errors.

Computerized database (BioDBx)

The collected data was transferred to a clinical database (BioDBx) for analysis. Our Head and Neck SPORE has developed and instituted this powerful integrated database with an outstanding record of data collection, management, and analysis. BioBDx runs on a dedicated server, is firewall protected, and supported by the University of Michigan Medical Center Information Technology department and Center of Advancement of Clinical Research. It is linked to the Health System clinical database (Careweb) for automatic download of clinical and demographic data and tracking of patient visits. Each patient entered in this database had identity protection through assignment of a unique identifying number. Categories of data entry included patient demographics, tumor site, tumor staging characteristics, health habits: tobacco use (cigarette smoking with average pack years: current, former (quit within 1 month vs. > 1 month) and never; alcohol use (AUDIT score), and HPV16 status for oropharyngeal primaries), treatment and detailed clinical follow-up. Our SPORE Program Tissue Core uses this same data management system for specimen tracking.

Data collection on various medications use

We searched for usage of all known members of each antacid class under their various generic and propriety names. Only usage documented after diagnosis date was counted. Within H2RA: cimetidine (Tagamet), ranitide (Zinetac, Zantac), famotidine (Pepcidine, Pepcid), and nizatidine were included. Within PPIs: omeprazole (Prilosec, Zegerid, Losec), pantoprazole (Protonix, Somac, Zurcal), esomeprazole (Nexium, Esotrex), lansoprazole (Prevacid, Zoton, Levant), rabeprazole (Zechin, Rabecid, AcipHex), and dexlansoprazole (Kapidex, Dexilant) were included.

Statistical analysis

We performed general survival analyses using Cox proportional hazards models to investigate which clinical factors and health behaviors measured by our SPORE Epidemiology project were associated with overall survival (OS), disease-specific survival (DSS), time-to-recurrence, and patterns of relapse that included local recurrence, regional, or distant metastasis in these patients with HNSCC. The development of second primary cancers was also assessed. These patients were censored at time of diagnosis of second primary in analyses of disease-specific survival, time-to-recurrence, and patterns of relapse. We created multivariable models using available covariates such as age, clinical stage, primary disease site, treatment modality, smoking status, etc. We tested whether PPI and/or H2RA usage adds to the prognostic ability of our time-to-event models using a likelihood ratio test. HRs and their 95% confidence intervals (CI) were estimated to quantify the magnitude and direction of any associations.

Pairwise comparisons between PPI and H2RA use and other characteristics were explored. The following variables were analyzed for association with medication usage: gender, age, race, marital status, education, income, tumor site, stage, smoking and drinking history, and primary treatment. Pearson χ^2 was used for categorical data and student t test for continuous data. All P values reported correspond to two-sided comparisons.

Cox proportional hazard models were used for survival outcomes (including time to recurrences). Multivariable models using all covariates and also parsimonious analysis using only covariates which displayed significant relationships in bivariate analysis or were *a priori* determined to be scientifically important were performed. A subset analysis of PPI/H2RA use and outcomes according to HPV status was performed among patients with oropharyngeal cancers that had available tissues for HPV16 testing. Survival time was defined as the time from diagnosis to death or last follow-up. Death from any cause was defined as an event for OS, only death from cancer was defined as an event for DSS. A recurrence event in the time-to-recurrence analysis was

defined as any recurrence (local, regional, and/or distant). All statistical analyses were done in SAS version 9.2 (SAS Institute). A two-tailed P value ≤ 0.05 was considered statistically significant.

Results

Cohort characteristics

From an initial 884 cases enrolled in our Head and Neck SPORE epidemiology project, 706 were treated at University of Michigan Hospital and were eligible for this study of medication usage. After further review of the medical record, other reasons for exclusion included: withdrawn of consent ($n = 1$), nonsquamous cell cancer ($n = 2$), unknown primary or nasal cavity primary ($n = 2$), unresectable or palliation ($n = 25$), incomplete clinical information ($n = 65$), treatment for HNSCC before enrollment ($n = 5$), cancer *in situ* ($n = 8$), multiple primaries ($n = 2$). Thus, our analyses for association between clinical data and use of various antacid medications was performed on a total of 596 previously untreated patients, diagnosed and treated at the University of Michigan for HNSCC between January 29, 2003 and November 7, 2008. The sociodemographics and clinicopathologic characteristics of this cohort are summarized in Table 1. The majority of cases were patients with advanced stage disease (stage III or IV cases = 482, 81%); 244 cases (41%) were stage T0, T1, or T2; 305 cases (51.7%) T3 or T4; and no T staging was possible in 44 cases (7.4%). The male/female ratio was 3:1 (448 males, 75% versus 148 females, 25%), average age: 58 years (range 21–92); average age by gender: 59.4 (females) versus 59.7 (males) years. By primary tumor sites: 150 cases (25%) of oral carcinomas, 251 cases (42%) of oropharyngeal carcinomas, 135 cases (23%) of hypopharynx and laryngeal carcinomas, and 58 cases (10%) in other head and neck sites (e.g., sinus, nasopharynx). The majority of patients had higher education (56%, with some college or more), 91% lived in counties with median income over 30,000 per year. There were 170 tumor recurrences and 222 deaths observed during follow-up; 28 patients presented with a second primary during follow-up (typically we consider a cancer a second primary if it is >2 cm from the original primary or it has been at least 3 years since the original primary was diagnosed). The Kaplan–Meier estimate for OS was 73% at 2 years and 59% at 5 years. Median follow-up time for OS was 55 months with a 95% CI of 50–60 months. HNSCC conventional treatment was categorized according with standard treatment modalities: surgery-only 68 cases (11%), radiation-only 31 cases (5%), surgery + radiation 75 cases (13%), radiation + chemotherapy 246 cases (41%), radiation + chemotherapy + surgery 176 cases (30%); there were no cases treated by chemotherapy alone, nor by a combination of surgery + chemotherapy.

Antacids usage and its impact on the clinical outcome of HNSCC patients

We defined users of antacid drugs in our association analyses as only those patients who had antacid usage documented after diagnosis date. Out of the 596 patients, 191 cases (32%) used only PPIs after diagnosis, 83 cases (14%) used only H2RAs, and 136 cases (23%) used both (H2RA + PPI) sometime after diagnosis (Table 2A). We also collected data on drug class use before diagnosis (recorded as "prior use"). Most patients with prior use continued to use PPIs after diagnosis but a small proportion of patients with prior use had no records of use after diagnosis date. Ten of 16 patients with records of prior H2RA use did not have records of H2RA use within 2 years after diagnosis and consequently were categorized as nonusers for analysis. "Late-post use" was recorded when the first record of antacid use dated more than 2 years after diagnosis and these patients were not included as PPI or H2RA users in our analysis. Frequencies of "prior" and "late-post" users of antacid drug classes are summarized in Table 2B.

The analyses were done initially using any H2RA use and any PPI use separately as predictors. We then created a categorical variable combining the information from both drug classes into 4 categories: PPI use only, H2RA use only, PPI and H2RA use, and no antacid use. The bivariate demographic information of our cohort by these categories are summarized in Table 3.

Clinical significance of H2RA usage

Our analysis of H2RA usage and its potential therapeutic benefit identified 219 patients (37%) who received H2RAs within 2 years of diagnosis with HNSCC. These patients received cimetidine ($n = 16$), ranitidine ($n = 215$), famotidine ($n = 37$; note that we did not find any nizatidine usage).

Bivariate demographic. Our analysis indicated a statistically significant association ($P < 0.05$) between H2RA usage and primary HNSCC tumor site, treatment modality, and patient education (Table 3).We observed higher H2RA use in patients with primary disease site in the oral cavity among all HNSCC sites, with higher education, and among those with trimodal (surgery, radiation and, chemotherapy) treatment. H2RA usage was lowest among those treated with radiation only. We also observed more frequent H2RA usage in patients with higher T stage (48% in T3, 4 vs. 31% in T0, T1, T2). Patients on H2RAs had a lower average age at diagnosis (57 vs. 59 years), but the distribution of ages across both groups was not notably different after closer look.

Patient survival and H2RA intake. In univariate analysis, we observed that patients taking H2RA had significantly better OS ($P = 0.0479$; Fig. 1A); when we considered drugs individually (cimetidine, ranitide, famotidine), this association was not maintained for any one particular drug. The statistical significance of the association with OS proved stronger in multivariable analysis after controlling for potential confounding variables such as age, gender, tumor site, stage, smoking, socioeconomic status, and treatment ($P = 0.02$; HR (95% CI): 0.67 (0.47–0.95); Table 4). In addition, when a backward selection algorithm was used to choose a best multivariable prediction model, H2RA usage was consistently chosen as a significant predictor of survival along with age, primary tumor site, and smoking

Table 1. Sociodemographic and clinicopathologic characteristics of the HNSCC cohort

Numerical measure	Mean (SD), median	Range
Age, y	57.9 years (11.2), 57 years	21–92
Categorical measures	***n* (%)**	
Gender		
Male	448 (75%)	
Female	148 (25%)	
Primary tumor subsite		
OC	150 (25%)	
OP	251 (42%)	
LA, HP	135 (23%)	
Other	58 (10%)	
Stage		
Early (CIS, I, II)	110 (19%)	
Late (III, IV)	482 (81%)	
T stage		
0,1,2	244 (41%)	
3,4	305 (52%)	
X,x	44 (7%)	
Smoking		
Never	145 (24%)	
Former (quit >1 month)	226 (38%)	
Current (quit within 1 month)	223 (38%)	
Race		
European American/white	560 (94%)	
Non-white	34 (6%)	
Married, Yes/No		
Married	369 (62%)	
Not married	223 (38%)	
Education		
HS or less	236 (44%)	
Some college or more	305 (56%)	
Treatment		
Surgery-only	68 (11%)	
Radiation-only	31 (5%)	
Surgery + radiation	75 (13%)	
Radiation + chemotherapy	246 (41%)	
Radiation, chemotherapy, and surgery	176 (30%)	

NOTE: The study included 596 previously untreated patients with HNSCC that were enrolled in the epidemiology program of the University of Michigan Head and Neck Cancer Specialized Program of Excellence in Research (SPORE) from 2003–2008. The International Classification of Diseases for Oncology (ICD-9 codes) based on the Union for International Cancer Control (UICC) standard classification criteria for head and neck tumors were used. Pct may not add to 100% due to rounding.
Abbreviations: CIS: carcinoma *in situ*; HP, hypopharynx; HS: high school; LA, larynx; NP: nasopharynx; OC, oral cavity; OP, oropharynx; X, unknown.

status. In the whole cohort of patients, we did not find evidence of a benefit of H2RA use for recurrence-free survival.

Interestingly, subset analysis of the patients with oropharyngeal carcinomas and available HPV16 status indicated H2RA usage as prognostic for better recurrence-free survival in multivariate analysis after controlling for HPV16 [$P = 0.03$; HR (95% CI) = 0.34 (0.12–0.92)].

Clinical significance of PPI usage

Our analysis of PPI usage identified 327 patients who received PPI within 2 years of diagnosis of HNSCC (55% of

Table 2. Antacid drug usage in 596 patients with HNSCC

A: Drug usage documented after diagnosis date in this cohort of previously untreated patients with HNSCC

Family of drugs	*N* % (out of 596)
PPI alone	191 (32%)
H2RA alone	83 (14%)
PPI and H2RA	136 (23%)
No record of usage	186 (31%)
Total	596 (100%)

B: Prior- and late-post drug usage in this cohort of previously untreated patients with HNSCC

Family of drugs	Prior use	Prior use with no post use	Late-post use
PPI	40	4	42
H2RA	16	10	26
Combination of both	13	1	8

NOTE: The data collection on the administration of the drugs of interest was conducted independently by three investigators. Drug usage of all known members of each antacid class under their various generic and propriety names was identified using a custom designed software program EMERSE (Electronic Medical Record Search Engine) and users of antacid drugs in our association analyses were defined as only those patients who had antacid usage documented after diagnosis date.

the total 596 patients). These patients received omeprazole ($n = 179$, 30%), lansoprazole ($n = 115$, 19.3%), esoprazole ($n = 104$, 17.45%), pantoprazole ($n = 127$, 21.3%), and rabeprazole ($n = 10$, 1.7%). Note that we did not find any dexlansoprazole usage.

Bivariate demographic. Our analysis indicated statistically significant associations between PPI usage and primary HNSCC tumor site and marital status (Table 3). We observed higher PPI usage in patients with primary disease site in the oropharynx and in those who were married.

Patient survival and PPI intake. We observed in univariate analysis that patients taking PPI had significantly better OS ($P < 0.0001$; Fig. 1B); this also was observed in multivariate analysis [$P < 0.0001$; HR (95% CI) = 0.55 (0.40–0.74); Table 4]. The statistical significance of the association proved stronger after controlling for potential confounding variables. Interestingly, when we considered drugs individually, this association with OS was maintained for omeprazole ($P = 0.0008$) and esomeprazole ($P = 0.001$); only a trend was noted for lansoprazole ($P = 0.06$) while pantoprazole did not demonstrate a significant association ($P = 0.67$). Univariate analysis failed to demonstrate an association or a trend between PPI use and unadjusted recurrence-free survival [$P = 0.39$; HR (95% CI) = 0.83 (0.60–1.14); Table 4]. However, there was a trend for better recurrence-free survival in PPI users in multivariate analysis after controlling for potential confounding variables such as age, gender, tumor site, stage, smoking, socioeconomic status, and treatment [$P = 0.06$; HR (95% CI) = 0.71 (0.50–1.01); Table 4]. In addition, when a backward selection algorithm (with stay criteria $\alpha = 0.10$) was used to choose a best multivariable prediction model, PPI usage was consistently chosen as a significant predictor of recurrence-free survival, along with age, smoking status, and treatment.

Clinical significance of H2RA ± PPI usage

Our analysis identified 136 patients who received both PPI and H2RA within 2 years of diagnosis of HNSCC (23% of the total 596 patients).

Bivariate demographic. Our analysis indicated a statistically significant association between H2RA + PPI usage and age, smoking, and treatment modality. Higher incidence of combined H2RA + PPI was observed in those that quit within 1 month and those who received trimodal therapy. Only a trend was noted in relation with primary HNSCC tumor site ($P = 0.08$) and median income level ($P = 0.06$).

Patient survival and H2RA+PPI intake. We observed that patients taking H2RA + PPI had significantly better OS than patients taking no antacid at all ($P < 0.0001$; Fig. 1C), and than those taking H2RA alone ($P = 0.05$); we failed to find evidence that the combination was better than PPI alone ($P = 0.88$) in univariate analysis. We did not find evidence of better recurrence-free survival in patients taking H2RA + PPI.

Discussion

To our knowledge, this is the first epidemiologic study that indicates therapeutic benefit of common antacid medication intake in patients with head and neck cancer. Our findings in this large epidemiologic cohort study indicate that clinical usage of the two classes of antacids (PPIs and H2RAs) after diagnosis with HNSCC may have significant benefit by enhancing patient survival. It is known that antacid medications have the ability to decrease and/or

Table 3. Bivariate demographic information by patients' intake of PPI and H2RA, alone and in combination

Characteristic		Overall ($N = 596$)	PPI alone ($N = 191$)	H2RA alone ($N = 83$)	PPI and H2RA ($N = 136$)	None ($N = 186$)
Age, y	Mean (SD), median, range among users	58.3 (11.3), 57, 21–92	59.2 (10.4), 58, 33—86	57.2 (12.2), 55, 21–86	56.3 (11.2), 55, 22–85	58.2 (11.4), 57, 27–92
	P		**0.06**	0.56	**0.05**	0.72
		Overall	**PPI alone *N* (% users)**	**H2RA alone, *N* (% users)**	**PPI+H2RA *N* (% users)**	**None *N* (% users)**
Gender	Male	448	152 (34%)	60 (13%)	98 (22%)	138 (31%)
	Female	148	39 (26%)	23 (16%)	38 (26%)	48 (32%)
	P		0.09	0.51	0.34	0.71
Primary tumor site	OC	150	32 (21%)	43 (29%)	43 (29%)	32 (21%)
	OP	251	67 (27%)	29 (12%)	60 (24%)	95 (38%)
	HP, LAR	135	65 (48%)	8 (6%)	23 (17%)	39 (29%)
	NP, other, unknown	58	27 (47%)	2 (3%)	10 (17%)	19 (33%)
	P		<0.0001	<0.0001	0.08	0.01
Stage	Early	110	42 (38%)	16 (15%)	19 (17%)	33 (30%)
	Late	482	148 (31%)	66 (14%)	117 (24%)	151 (31%)
	Missing	4				
	P		0.13	0.82	0.12	0.79
T stage	0,1,2	244	78 (32%)	31 (13%)	51 (21%)	84 (34%)
	3,4	305	96 (31%)	48 (16%)	78 (26%)	83 (27%)
	X,x	44	17 (39%)	3 (7%)	7 (16%)	17 (39%)
	Missing	3				
	P		0.63	0.22	0.22	0.10
Smoking	Never	145	39 (27%)	17 (12%)	45 (31%)	44 (30%)
	Former	226	77 (34%)	33 (15%)	45 (20%)	71 (31%)
	Current-quit within 1 month	223	75 (34%)	32 (14%)	46 (21%)	70 (31%)
	Missing	2				
	P		0.30	0.70	0.03	0.97

(Continued on the following page)

Table 3. Bivariate demographic information by patients' intake of PPI and H2RA, alone and in combination (Cont'd)

		Overall	PPI alone *N* (% users)	H2RA alone, *N* (% users)	PPI+H2RA *N* (% users)	None *N* (% users)
Race	White	560	178 (32%)	79 (14%)	131 (23%)	172 (31%)
	Non-White	34	13 (38%)	3 (9%)	5 (15%)	13 (38%)
	Missing	2				
	P		0.43	0.39	0.24	0.36
Married (Yes/No)	Married	369	138 (37%)	49 (13%)	81 (22%)	101 (27%)
	Not married	223	53 (24%)	33 (15%)	54 (24%)	83 (37%)
	Missing	4				
	P		0.0006	0.60	0.52	0.01
Education some college	HS or less	236	74 (31%)	42 (18%)	50 (21%)	70 (30%)
	Some college or more	305	102 (33%)	34 (11%)	74 (24%)	95 (31%)
	Missing	55				
	P		0.61	0.03	0.40	0.71
County median income from census	30,000 or below	55	16 (29%)	8 (15%)	7 (13%)	24 (44%)
	Above 30,000	541	175 (32%)	75 (14%)	129 (24%)	162 (30%)
	P		0.62	0.89	0.06	0.04
Treatment	Surgery only	68	25 (37%)	18 (26%)	9 (13%)	16 (24%)
	Radiation only	31	15 (48%)	1 (3%)	3 (10%)	12 (39%)
	Surgery + radiation	75	24 (32%)	13 (17%)	16 (21%)	22 (29%)
	Radiation + chemotherapy	246	79 (32%)	20 (8%)	50 (20%)	97 (39%)
	Radiation + chemotherapy + surgery	176	48 (27%)	31 (18%)	58 (33%)	39 (22%)
	P		0.18	<0.0003	0.001	0.002

NOTE: The patients in PPI + H2RA treatment group have been excluded from PPI alone and H2RA alone groups. All statistical analyses were done in SAS version 9.2 (SAS Institute). A two-tailed $P \leq 0.05$ was considered statistically significant.

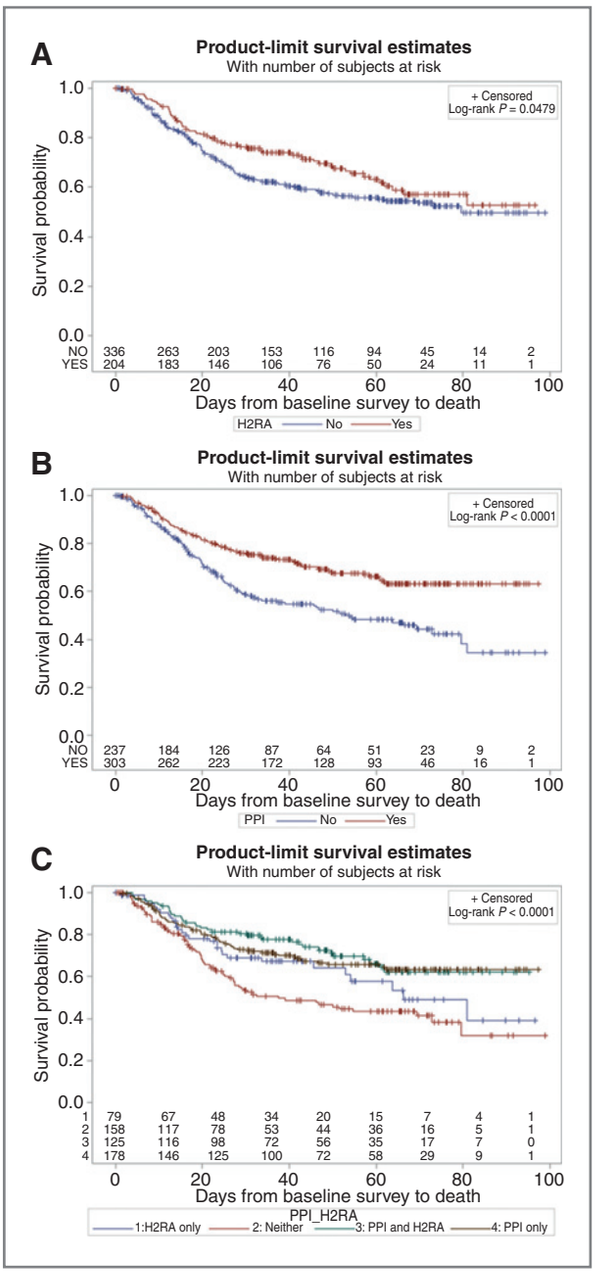

Figure 1. Survival benefits according with intake of antacids in patients with HNSCC. A, unadjusted OS in relation with usage of H2RA (A) and PPIs (B). C, each antacid class alone and in combination versus nonusers. Median follow-up = 55 months; 95% CI, 50–60 months.

inhibit the production of gastric acid and are commonly and chronically used in patients with HNSCC for the management of their gastroesophageal reflux disease. However, the potential effects of antacid medications and any potential mechanisms for altering HNSCC progression and outcome are unknown. Identifying molecular mechanisms associated with HNSCC progression and metastasis is key to improving clinical outcomes.

HNSCC are marked by their aggressiveness and invasiveness (5). HNSCC are known for poor clinical outcomes with mortality among the highest of all carcinomas mainly due to the development of metastatic disease (11, 12). The ability for cancer to metastasize seems to associate with the expression of endothelial adhesion molecules ligands by circulating tumor cells that allow them to bind to the endothelium lining the vasculature initiating extravasation (13, 14). Sialyl Lewis X (sLeX) is an endothelial adhesion molecule known to play the key role in the initiation of the metastatic spread in gastrointestinal cancers by initiating dissemination through direct interaction with E-selectin expressing endothelium (15). In agreement with findings from other types of human cancer (e.g. gastric, breast, colon; refs. 15–18), our previous studies have shown that cimetidine, the prototypical drug of the H2RAs, may have an effect on E-selectin, a molecule with critical roles in cancer dissemination (19). In addition, cimetidine seems to affect other players with important roles in tumor growth and progression (e.g. epithelial growth factor signaling pathway), and to prevent metastasis (20, 21, 22). Our *in vitro* analysis of a well-characterized set of human cell lines derived from the most common locations of the HNSCC indicates that oral squamous cell carcinomas expressed higher sLeX, which increases with advanced stage (23). Our current study has identified the highest H2RA usage in patients with oral carcinomas. It is interesting to note that in contrast to cimetidine, the most frequently prescribed H2RA drug in our cohort, ranitidine, has not proven to have similar effects as cimetidine (22); it is also known that the two also differ in molecular structure. In our patient cohort, cimetidine alone was used by only a few patients (16/596) compared with ranitidine (215/596). When analyzed per individual drug, despite the significant number of ranitidine users, our analysis failed to demonstrate the same benefit on patient survival as the entire H2RA class. Therefore, we postulate that H2RA drugs may differ in their mechanisms of action and may alter expression of other factors besides key endothelial adhesion molecules that could explain their clinical benefits in patients with HNSCC.

Remarkably, our analysis identified H2RA class usage as significant prognostic factor for recurrence-free survival only in patients with oropharyngeal tumors positive for HPV16. HPV has recently emerged as the primary etiologic factor for patients with tumors in the oropharynx that are also associated with younger age at diagnosis; 65% to 85% of the oropharyngeal cancers diagnosed this year in the United States are HPV-related with 3-year failure rates of 30% to 36% (24–31). Consequently, unique pathologic profiles have emerged that are consistent with the changing incidence of HNSCC (32–34). Patients with HPV^{+}head and neck cancer have a distinct risk profile, associated with a less remarkable history of tobacco and alcohol use (35, 36), a more beneficial micronutrient profile (37), improved cellular immunity (38), and improved survival compared to those with HPV^{-} tumors (39–42). Notably, a significant subset (20% 30%) of HPV^{+} tumors fails to respond to therapy and recur principally as distant metastases. Studies

Table 4. PPI and H2RA usage and patient OS and time to recurrence

		Characteristics			
		OS univariate	**OS Multivariable**	**Recur univariate**	**Recur multivariable**
PPI Usage	Yes	0.55 (0.42–0.73)	0.55 (0.40–0.74)	0.83 (0.60–1.14)	0.71 (0.50–1.01)
	No	Ref.	Ref.	Ref.	Ref.
	P	<0.0001	<0.0001	0.39	0.06
H2RA Usage	Yes	0.74 (0.55–1.00)	0.67 (0.47–0.95)	1.02 (0.73–1.42)	0.90 (0.61–1.34)
	No	Ref.	Ref.	Ref.	Ref.
	P	0.0479	0.02	0.92	0.61
Gender	Male	1.14 (0.82–1.59)	1.30 (0.90–1.88)	1.09 (0.74–1.61)	0.94 (0.62–1.42)
	Female	Ref.	Ref.	Ref.	Ref.
	P	0.42	0.16	0.68	0.75
Primary tumor site	OC	1.43 (1.02–2.00)	2.44 (1.50–3.96)	1.26 (0.84–1.87)	1.90 (1.12–3.23)
	HP, LAR	1.43 (0.99–2.06)	1.43 (0.94–2.18)	1.35 (0.90–2.02)	1.45 (0.92–2.29)
	NP, other, unknown	0.86 (0.50–1.47)	1.11 (0.62–2.00)	0.73 (0.38–1.43)	1.03 (0.50–2.13)
	OP	Ref.	Ref.	Ref.	Ref.
	P	0.05	0.004	0.22	0.08
Stage	Late	1.65 (1.09–2.49)	1.59 (0.97–2.60)	1.79 (1.10–2.94)	1.14 (0.65–1.98)
	Early	Ref.	Ref.	Ref.	Ref.
	P	0.02	0.07	0.02	0.65
Smoking status	Never	0.44 (0.30–0.66)	0.51 (0.33–0.79)	0.42 (0.26–0.67)	0.48 (0.29–0.79)
	Former	0.72 (0.53–0.98)	0.62 (0.44–0.88)	0.80 (0.57–1.14)	0.73 (0.49–1.07)
	Current-quit within 1 month	Ref.	Ref.	Ref.	Ref.
	P	0.0002	0.003	0.002	0.01
Education some college	HS or less	Ref.	Ref.	Ref.	Ref.
	Some college or more	0.72 (0.54–0.96)	0.83 (0.61–1.13)	0.78 (0.56–1.09)	0.92 (0.64–1.31)
	P	0.02	0.24	0.14	0.64
County median income from census					
	30,000 or below	1.61 (1.05–2.47)	1.16 (0.71–1.90)	1.70 (1.05–2.75)	1.36 (0.79–2.33)
	Above 30,000	Ref.	Ref.	Ref.	Ref.
	P	0.03	0.55	0.03	0.27
Treatment	Surgery only	0. 56 (0.33–0.96)	0.39 (0.20–0.78)	0.16 (0.06–0.44)	0.12 (0.04–0.35)
	Radiation only	0.26 (0.08–0.83)	0.22 (0.06–0.74)	0.08 (0.01–0.55)	0.07 (0.01–0.51)
	Surgery + radiation	1.13 (0.74–1.73)	0.56 (0.34–0.93)	0.67 (0.40–1.25)	0.44 (0.24–0.80)
	Radiation + chemotherapy	1.05 (0.76–1.45)	0.96 (0.66–1.39)	0.71 (0.50–1.01)	0.75 (0.50–1.12)
	Radiation + chemotherapy+ surgery	Ref.	Ref.	Ref.	Ref.
	P	0.03	0.009	0.0004	<0.0001
Age, y	10-year increase	1.43 (1.26–1.62)	1.60 (1.38–1.86)	1.02 (1.01–1.04)	1.03 (1.01–1.05)
	P	<0.0001	<0.0001	0.006	0.0004

NOTE: OS and time to recurrence were analyzed using log-rank for univariate analysis and Cox proportional hazards models for multivariate analysis. All statistical analyses were done in SAS version 9.2 (SAS Institute). A two-tailed $P \leq 0.05$ or less was considered statistically significant. HR followed by the 95% CI values between parentheses are provided. Abbreviations: HP, hypopharynx; HS, high school; LA, larynx; NP, nasopharynx; OC, oral cavity, OP, oropharynx; Recur, time to recurrence.

conducted at the University of Michigan have made significant contributions to the understanding of the impact of HPV infection on the pathobiology of HNSCC and response to therapy (40–41). Our current clinical findings have prompted laboratory studies to explore potential mechanisms of the correlations observed clinically using the HPV^+ versus HPV^- carcinoma–derived cell lines from our large SPORE collection.

The major challenge in the management of patients with HNSCC today is the development of evasive resistance to conventional therapies. Our recent evidence demonstrates that cancer stem cells (CSC) play a critical role in the development of metastases in HNSCC and that sLex can help identify the metastatic CSC subset (23). Malignant progression in cancer requires populations of CSCs endowed with unlimited self-renewal, survival under stress and low pH, and establishment of distant metastases. It is also known that increasing tumor mass leads to an acidic tumor microenvironment, while acidity contributes to both tumor progression and resistance to chemotherapy (42, 44). Tumor cells are capable of maintaining a fine state of homeostasis with normal intracellular pH despite the acidic extracellular milieu because of proton pumps expressed in their plasma membranes. A key mechanism to counteract the cytosolic acidification is active proton extrusion by proton pumps. This causes intracellular alkalinization and extracellular acidification, which creates a pH gradient. Low pH of the extracellular microenvironment promotes the secretion and activation of proteolytic enzymes, and release of proangiogenic factors contributing to neovessel formation, cancer invasion, and metastasis (45, 46). This pH gradient also has been associated with multidrug resistance, likely from drug sequestration and neutralization in the acidic organelles or in the acidic extracellular environment (47, 48). Although several pH regulatory mechanisms are operating in tumor cells (Na^+/H^+ exchangers, carbonic anhydrases, bicarbonate transporters, H^+-linked monocarboxylate transporters), the major mechanism is represented by the proton pumps such the vacuolar ATPase (V-ATPase) that are ubiquitously expressed on the plasma membrane of the tumor cells. Highly metastatic cells preferentially use V-ATPases, suggesting that the proton pumps are critical for acquisition of a more metastatic and invasive phenotype (48, 49). Therefore, disruption of this pH gradient with PPIs may be an important antimetastatic mechanism.

Although the specific targets of PPIs are H^+-ATPases contained within the lumen of gastric parietal cells, PPIs also inhibit the activity of V-ATPases, thus broadly blocking proton transport across membranes through the entire body. Our study identified that patients with HNSCC take PPIs, more often alone rather than in combination with H2RA, to treat symptoms that accompany conventional therapeutic regimens, and that their usage may lead to a better patient overall and recurrence-free survival with a higher ratio than with the H2RA use alone or of the combination of both. Interestingly, among the various class members, individual drug usage of only omeprazole and esomeprazole maintained the same survival benefit. At this time we do not fully understand the complex biologic mechanisms by which antacid medications may influence patient outcome. Death from other causes and comorbidities is a major contributor to poor OS rates in patients with head and neck cancer, thus it is possible that PPIs and H2RAs influence deaths from other causes. Studies are currently underway in our laboratory to seek biologic evidences (e.g., potential effects on tumor cells and stroma, modulation of microenvironment, effects on immunity, etc.) in support of the significant association with improved patient outcome observed in the clinical settings.

Elucidation of the novel link between the pathobiology of HNSCC and antacid medication use could lead to important new chemopreventive strategies for patients with HNSCC, for whom the current preventive armamentarium is still limited. HNSCCs are an ideal model for the study of chemoprevention because they follow a histopathologic progression from normal tissue to hyperplasia to severe dysplasia to carcinoma *in situ* to invasive and metastatic carcinomas. Moreover, the phenomenon of field cancerization is well understood in HNSCC, having been characterized first in oral cancer (50). Because of this retained risk for cancer development in the epithelium adjacent to primary disease, second primary tumors act as a possible target for secondary chemoprevention in patients previously diagnosed and treated for HNSCC; furthermore, oral premalignant lesions could also serve as prime targets for chemopreventive agents.

This is the first study to report an association of the PPI and H2RA class of drugs with treatment outcomes and survival in patients with HNSCC. Despite the limitations of the current study (absence of randomization), the intriguing associations observed in our cohort will deserve further validation in randomized prospective trials to provide comprehensive support for a novel therapeutic approach that could be readily translated into clinical benefit. Further elucidation of the mechanisms of action is necessary to determine whether the beneficial effects might be extrapolated to other types of cancer. A series of focused clinical trials will be necessary to further evaluate the antacids anticancer potential in clinical settings, with the ultimate goal of improving the outcome of patients afflicted with HNSCC. If confirmed in prospective studies, new chemopreventive approaches may be possible with drugs that have a favorable therapeutic ratio and are readily available in the clinical settings.

Disclosure of Potential Conflicts of Interest

G.T. Wolf is a consultant/advisory board member for IRX Therapeutics. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

None of the funding sources had any role in the design, conduct, or interpretation of the experiments.

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Grant Support

This study was supported by the NCI/NIDCR P50 CA097248 [University of Michigan Head and Neck Cancer Specialized Program of Research Excellence (SPORE, Principal Investigator (PI): Gregory Wolf), the Research Scholar Grant RSG-13-103-01–CCE from the American Cancer Society (PI: Silvana Papagerakis), and Undergraduate Research Opportunity Program at the University of Michigan (Ann Arbor, MI).

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Received January 9, 2014; revised September 15, 2014; accepted September 28, 2014; published online December 2, 2014.

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