



Statin use associated with improved overall and cancer specific survival in patients with head and neck cancer

Abhinav Gupta^a, William Stokes^a, Megan Eguchi^{b,1}, Mohammad Hararah^c, Arya Amini^d, Adam Mueller^a, Rustain Morgan^e, Cathy Bradley^b, David Raben^a, Jessica McDermott^f, Sana D Karam^{a,*}

^a Department of Radiation Oncology, University of Colorado, Denver, United States

^b Department of Health Systems, Management, and Policy, Colorado School of Public Health, United States

^c Department of Otolaryngology, University of Colorado, Denver, United States

^d Department of Radiation Oncology, City of Hope Medical Center, United States

^e Department of Radiology, University of Colorado, Denver, United States

^f Department of Medicine, Division of Medical Oncology, University of Colorado, Denver, United States

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ABSTRACT

Objectives: Studies have shown the utility of lipid-lowering agents in improving outcomes in various cancers. We aim to explore how statins affect overall survival and cancer specific survival in head and neck cancer patients using population-based datasets.

Patients and methods: Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset, we separated HNC patients into three groups: those with no hyperlipidemia (nH), those with hyperlipidemia and not taking a statin (HnS), and those with hyperlipidemia and taking a statin (H + S). Overall survival (OS) and cancer specific survival (CSS) were compared between the three groups based on disease subsite (oral cavity, oropharynx, and other) using Kaplan-Meier and multivariate Cox regression analysis (MVA), controlling for demographic, socioeconomic, staging, treatment, and comorbidity covariates. Using Pearson chi-square analysis, we also compared the incidence of cancer-related toxicity events.

Results: There were 495 nH, 567 HnS, and 530 H + S patients. H + S patients had superior OS and CSS (73.0, 81.2%) relative to nH (58.6, 69.1%) and HnS groups (61.7, 69.2%) ($p < 0.01$). On MVA, H + S patients showed improved OS ($p < 0.01$) and CSS ($p = 0.04$) compared to nH (HR = 1.64, 1.56) and HnS (HR = 1.40, 1.37). MVA stratified by subsite yielded similar results for oral cavity and oropharyngeal disease. Toxicity-related events did not differ significantly between the groups.

Conclusion: HNC patients with hyperlipidemia and taking a statin demonstrated improved outcomes compared to nH and HnS patients, further supporting statins' role as a potential adjuvant anti-neoplastic agent in HNC. Further prospective studies to investigate the impact of statins on HNC outcomes are warranted.

Introduction

Although there has recently been an advancement of therapeutic modalities for head and neck cancer (HNC) [1], survival rates have remained low. In the face of poor prognosis, clinicians have begun to explore how dysregulation of metabolic systems impacts outcomes. One area of interest is the relationship between lipid metabolism and tumor growth, risk of metastasis, and overall survival.

Lipids are traditionally divided into two groups: lipoid, which include cholesterol (and other sterols) and phospholipids; and fat, which

include triglycerides [2]. Hyperlipidemia is defined by elevated levels of triglycerides, total cholesterol, and lipoproteins such as LDL, VLDL, and is associated with a variety of diseases.

Many studies across different cancer types have demonstrated the relationship between hyperlipidemia and carcinogenesis [3–5]. Higher lipid levels, for example, have been shown to be an unfavorable prognostic factor in patients with small cell lung [6], and breast cancer [7]. Similarly, antihyperlipidemic agents, such as statins, have been shown to reduce cancer mortality [8] by interfering with cell signaling and promoting apoptosis [9].

* Corresponding author at: University of Colorado Denver | Anschutz Medical Campus, Aurora, CO-80045, United States.

E-mail addresses: MEGAN.EGUCHI@ucdenver.edu (M. Eguchi), sana.karam@ucdenver.edu (S.D. Karam).

¹ Statistical analysis performed by Megan Eguchi.

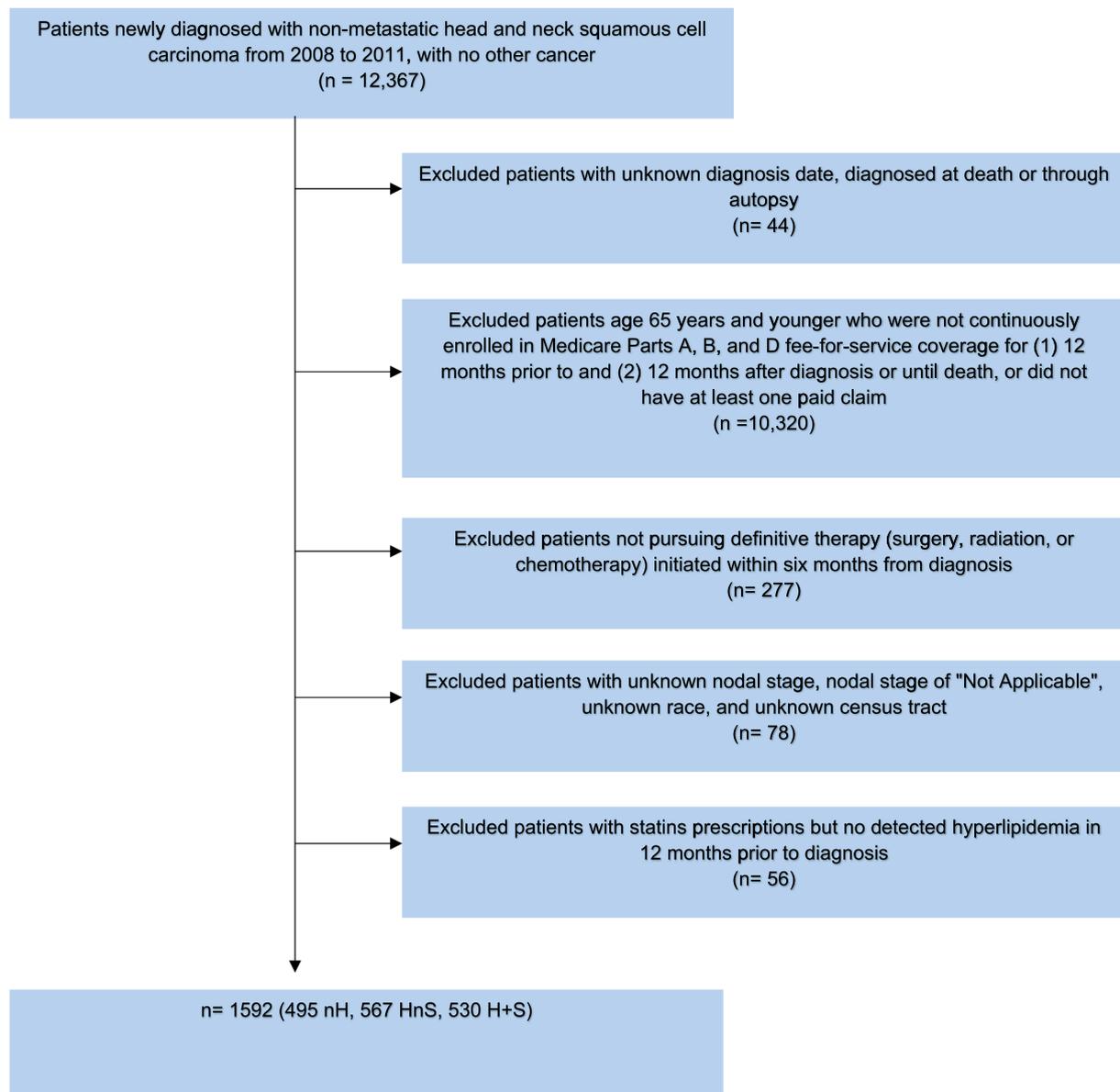


Fig. 1. Consort diagram

Lebo et al demonstrated improved overall survival (OS) and disease specific survival in patients with squamous cell carcinoma of the larynx, hypopharynx, and nasopharynx who incidentally took statins at the time of diagnosis [10]. Our study aims to include all head and neck cancer subsites; in addition, it explores statin use in HNC patients with diagnosed hyperlipidemia. We used the SEER-Medicare database to evaluate survival and toxicity outcomes among HNC patients with no hyperlipidemia (nH) vs. hyperlipidemia and not taking a statin (HnS) vs. hyperlipidemia and taking a statin (H + S).

Patients and methods

Data source

All patients were part of the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data set, which combines population based cancer registries with longitudinal Medicare data. SEER tracks

approximately 28% of the population [11] with information including demographics, tumor characteristics, treatment, socioeconomic status, mortality, and cause of death. Medicare similarly provides information about diagnosis and treatments, including medications and procedures, which are reported using the *International Classification of Diseases, Ninth Revision (ICD-9)*, *Clinical Modification* codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS). For each Medicare event that included a prescription medicine, a part D claim and date of service was filed.

Sample selection

From our initial group of patients with HNC, we selected those with non-metastatic squamous cell carcinoma (International Classification of Diseases for Oncology ICD-O-3 morphology codes 8050–8089) of the head and neck (ICD-O-3 topography codes C00-C14) diagnosed in 2008 to 2011 with no other cancer (n = 12,367). We selected the year 2008

Table 1
Patient characteristics.

		Total		nH		HnS		H + S		p (H + S vs. nH)	p (H + S vs. HnS)
		N	%	N	%	N	%	N	%		
All patients		1592	100.0	495	100.0	567	100.0	530	100.0	.	.
Age category	66–69	392	24.6	139	28.1	139	24.5	114	21.5	0.03	0.46
	70–74	440	27.6	123	24.9	158	27.9	159	30.0	.	.
	75 and older	760	47.7	233	47.1	270	47.6	257	48.5	.	.
Sex	Female	656	41.2	193	39.0	259	45.7	204	38.5	0.87	0.02
	Male	936	58.8	302	61.0	308	54.3	326	61.5	.	.
Race/ethnicity	White NH	1277	80.2	389	78.6	451	79.5	437	82.5	0.12	0.22
	Non-white or hispanic	315	19.8	106	21.4	116	20.5	93	17.6	.	.
Marital status	Non-married	861	54.1	294	59.4	311	54.9	256	48.3	0.00	0.03
	Married or partnered	731	45.9	201	40.6	256	45.2	274	51.7	.	.
Geographic region	East	272	17.1	59	11.9	119	21.0	94	17.7	0.07	0.33
	Midwest	205	12.9	65	13.1	70	12.4	70	13.2	.	.
	South	437	27.5	151	30.5	137	24.2	149	28.1	.	.
	West	678	42.6	220	44.4	241	42.5	217	40.9	.	.
Patient location	Metropolitan	1257	79.0	358	72.3	457	80.6	442	83.4	< 0.0001	0.23
	Non-metropolitan	335	21.0	137	27.7	110	19.4	88	16.6	.	.
Year of diagnosis	2008	370	23.2	120	24.2	135	23.8	115	21.7	0.53	0.76
	2009	378	23.7	125	25.3	127	22.4	126	23.8	.	.
	2010	385	24.2	111	22.4	137	24.2	137	25.9	.	.
	2011	459	28.8	139	28.1	168	29.6	152	28.7	.	.
Primary site ¹	Oral cavity	804	50.5	244	49.3	277	48.9	283	53.4	0.41	0.15
	Oropharynx	571	35.9	179	36.2	218	38.5	174	32.8	.	.
	Other	217	13.6	72	14.6	72	12.7	73	13.8	.	.
Tumor size stage	T0-1	457	28.7	128	25.9	167	29.5	162	30.6	< 0.0001	0.44
	T2	476	29.9	119	24.0	175	30.9	182	34.3	.	.
	T3-4	452	28.4	180	36.4	150	26.5	122	23.0	.	.
	Unknown	207	13.0	68	13.7	75	13.2	64	12.1	.	.
Nodal stage	N0	877	55.1	281	56.8	290	51.2	306	57.7	0.46	0.09
	N1	274	17.2	74	14.9	110	19.4	90	17.0	.	.
	N2-3	441	27.7	140	28.3	167	29.5	134	25.3	.	.
Comorbidity index	0	1001	62.9	345	69.7	354	62.4	302	57.0	< 0.0001	0.07
	1 or more	591	37.1	150	30.3	213	37.6	228	43.0	.	.
Most-visited facility was teaching hospital	No or unknown	725	45.5	229	46.3	268	47.3	228	43.0	0.30	0.16
	Yes	867	54.5	266	53.7	299	52.7	302	57.0	.	.
Tract pct high school only - above median	Not above median	790	49.6	238	48.1	282	49.7	270	50.9	0.36	0.69
	Above median	802	50.4	257	51.9	285	50.3	260	49.1	.	.
Tract pct below poverty - above median	Not above median	801	50.3	223	45.1	299	52.7	279	52.6	0.02	0.98
	Above median	791	49.7	272	54.9	268	47.3	251	47.4	.	.
Surgery	No	652	41.0	218	44.0	233	41.1	201	37.9	0.05	0.28
	Yes	940	59.1	277	56.0	334	58.9	329	62.1	.	.
Chemotherapy	No	867	54.5	272	54.9	296	52.2	299	56.4	0.64	0.16
	Yes	725	45.5	223	45.1	271	47.8	231	43.6	.	.
Radiation therapy	No radiation	554	34.8	164	33.1	185	32.6	205	38.7	0.06	0.04
	Radiation	1038	65.2	331	66.9	382	67.4	325	61.3	.	.
Metformin	No	1476	92.7	483	97.6	537	94.7	456	86.0	< 0.0001	< 0.0001
	Yes	116	7.3	12	2.4	30	5.3	74	14.0	.	.
Hypertension	No	378	23.7	224	45.3	95	16.8	59	11.1	< 0.0001	0.01
	Yes	1214	76.3	271	54.8	472	83.3	471	88.9	.	.
Diabetes	No	1112	69.9	418	84.4	378	66.7	316	59.6	< 0.0001	0.02
	Yes	480	30.2	77	15.6	189	33.3	214	40.4	.	.

¹ Other sites include hypopharynx, nasopharynx, pyriform sinus, salivary glands.

to ensure at least one year with the Medicare Part D claim data (it began in 2006) and 2011 for at least one year of follow-up. Patients with an unknown diagnosis, diagnosed at death, or diagnosed by autopsy were excluded (n = 44). To capture those with complete data, only patients who were 66 years and older and continuously enrolled in Medicare Parts A, B, and D fee-for-service coverage for 12 months prior and 12 months after diagnosis or until death and at least one paid claim were included (n = 2003). Then using CPT, HCPCS, ICD-9, and NDC codes reported in the Medicare Provider Analysis and Review (MEDPAR), Outpatient, National Claims History (NCH) Physician/Supplier, Durable Medical Equipment (DME), and Part D (PDESAF) claims, we identified patients undergoing definitive intent therapy. We defined this as surgery, radiotherapy, or chemotherapy initiated within 6 months of diagnosis (n = 1726). Patients who had unknown race,

census tract, nodal stage (or stage of “Not Applicable), were then excluded (n = 78). Lastly, patients with statin prescriptions but no ICD-9 code for hyperlipidemia in 12 months prior to diagnosis were excluded as well (n = 56), leaving a total of 1592 patients (Fig. 1).

Outcome measures

Common comorbidities that exist with dysregulated lipid metabolism, including diabetes mellitus, metformin use [12], chronic hypertension, and chronic kidney disease, were included as covariates. Prescription medications were identified using generic names, brand names, and NDC codes on PEDSAF claims, and use of these drugs was defined as three or more prescriptions filled in the year prior to diagnosis and three or more prescriptions filled in the year since diagnosis

Table 2A
Overall survival.

		Univariate Kaplan-Meier			Univariate cox PH			Multivariate cox PH			
		OS2	95% CI	p	HR	95% CI	p	HR	95% CI	p (class)	p (variable)
Hyperlipidemia and statins category	H + S	73.0%	69–76.6%	< 0.01	< 0.01
	nH	58.6%	54.1–62.8%	.	1.70	1.37–2.1	< 0.01	1.64	1.29–2.07	< 0.01	.
	HnS	61.7%	57.6–65.6%	.	1.52	1.23–1.88	< 0.01	1.40	1.12–1.74	< 0.01	.
5-year age categories	66–69	72.2%	67.5–76.4%	< 0.01	< 0.01
	70–74	74.1%	69.7–77.9%	.	0.93	0.72–1.21	0.59	1.04	0.8–1.36	0.78	.
	75 and older	55.0%	51.4–58.5%	.	1.85	1.49–2.29	< 0.01	2.03	1.61–2.55	< 0.01	.
Sex	Male	65.9%	62.8–68.9%	0.17	0.45
	Female	62.5%	58.7–66.1%	.	1.12	0.95–1.33	0.17	1.08	0.89–1.3	0.45	.
Race/ethnicity	White NH	65.5%	62.8–68%	0.14	0.59
	Non-white or hispanic	60.6%	55–65.8%	.	1.16	0.95–1.42	0.15	0.94	0.76–1.17	0.59	.
Marital status	Married or partnered	72.5%	69.1–75.6%	< 0.01	< 0.01
	Non-married	57.7%	54.3–60.9%	.	1.71	1.44–2.04	< 0.01	1.39	1.16–1.68	< 0.01	.
Geographic region	West	64.0%	60.3–67.5%	0.31	0.36
	East	66.5%	60.6–71.8%	.	0.92	0.73–1.17	0.51	0.78	0.59–1.03	0.08	.
	Midwest	69.3%	62.5–75.1%	.	0.85	0.64–1.12	0.24	0.87	0.63–1.19	0.38	.
	South	61.8%	57.1–66.2%	.	1.09	0.9–1.33	0.39	0.88	0.69–1.12	0.29	.
Patient location	Metropolitan	64.9%	62.2–67.5%	0.40	0.64
	Non-metropolitan	63.0%	57.6–67.9%	.	1.09	0.89–1.33	0.40	0.95	0.74–1.2	0.64	.
Year of diagnosis	2008	63.5%	58.4–68.2%	0.72	0.50
	2009	63.5%	58.4–68.1%	.	0.99	0.78–1.26	0.94	0.99	0.78–1.26	0.93	.
	2010	63.9%	58.9–68.5%	.	0.99	0.78–1.25	0.91	1.01	0.8–1.29	0.92	.
	2011	66.7%	62.2–70.8%	.	0.89	0.71–1.12	0.33	0.86	0.68–1.09	0.22	.
Primary site ¹	Oral cavity	68.0%	64.7–71.1%	< 0.01	0.06
	Oropharynx	62.7%	58.6–66.5%	.	1.22	1.02–1.47	0.03	0.75	0.6–0.95	0.02	.
	Other	56.2%	49.4–62.5%	.	1.53	1.21–1.93	< 0.01	0.86	0.66–1.13	0.27	.
Tumor size stage	T0-1	80.1%	76.1–83.5%	< 0.01	< 0.01
	T2	64.3%	59.8–68.4%	.	1.96	1.52–2.53	< 0.01	1.99	1.08–3.67	0.03	.
	T3-4	47.3%	42.7–51.9%	.	3.45	2.71–4.39	< 0.01	5.59	3.11–10.02	< 0.01	.
	Unknown	68.1%	61.3–74%	.	1.81	1.32–2.49	< 0.01	4.28	2.16–8.49	< 0.01	.
Nodal stage	N0	71.8%	68.7–74.7%	< 0.01	< 0.01
	N1	56.6%	50.5–62.2%	.	1.71	1.37–2.13	< 0.01	1.53	1.2–1.95	< 0.01	.
	N2-3	54.9%	50.1–59.4%	.	1.80	1.49–2.17	< 0.01	1.77	1.4–2.24	< 0.01	.
Comorbidity index	< 0.01	70.6%	67.7–73.3%	< 0.01	< 0.01
	1 or more	54.1%	50–58.1%	.	1.81	1.53–2.13	< 0.01	1.70	1.42–2.02	< 0.01	.
Most-visited facility was teaching hospital	No or unknown	61.4%	57.7–64.8%	0.01	0.03
	Yes	67.1%	63.9–70.1%	.	0.81	0.69–0.96	0.01	0.82	0.69–0.98	0.03	.
Tract pct high school only - above median	Not above median	67.1%	63.7–70.2%	0.02	0.01
	Above median	62.0%	58.5–65.2%	.	1.21	1.03–1.43	0.02	1.31	1.06–1.61	0.01	.
Tract pct below poverty - above median	Not above median	68.4%	65.1–71.5%	< 0.01	0.48
	Above median	60.6%	57.1–63.9%	.	1.33	1.13–1.57	< 0.01	1.07	0.88–1.31	0.48	.
Surgery	No	52.5%	48.5–56.2%	< 0.01	< 0.01
	Yes	72.9%	69.9–75.6%	.	0.49	0.41–0.58	< 0.01	0.33	0.21–0.52	< 0.01	.
Chemotherapy	No	68.9%	65.7–71.8%	< 0.01	0.27
	Yes	59.3%	55.6–62.8%	.	1.37	1.16–1.61	< 0.01	0.88	0.7–1.1	0.27	.
Radiation therapy	No radiation	74.2%	70.3–77.6%	< 0.01	< 0.01
	Radiation	59.3%	56.3–62.3%	.	1.68	1.39–2.03	< 0.01	0.30	0.19–0.49	< 0.01	.
Metformin	No	64.0%	61.5–66.3%	0.09	0.41
	Yes	71.6%	62.4–78.9%	.	0.74	0.52–1.05	0.09	0.78	0.64–0.95	0.41	.
Hypertension	No	68.0%	63–72.4%	0.07	0.16
	Yes	63.4%	60.6–66.1%	.	1.20	0.98–1.47	0.07	1.19	0.98–1.45	0.16	.
Diabetes	No	65.8%	63–68.5%	0.10	0.09
	Yes	61.5%	56.9–65.6%	.	1.16	0.97–1.38	0.10	1.18	0.94–1.49	0.09	.

1-Other sites include hypopharynx, nasopharynx, pyriform sinus, salivary glands.

Legend: OS2, percent 2-year overall survival; 95% CI, 95% confidence intervals; PH, proportional hazard; HR, hazard ratio.

(unless a patient died less than a year from diagnosis, in which case we required at least one prescription filled for every four months of survival). Chronic conditions including hypertension, chronic kidney disease, and diabetes were identified using the ICD-9 diagnosis codes used in the Chronic Conditions Data Warehouse algorithm with at least one diagnosis reported on a MEDPAR, outpatient, or NCH claim one year prior to diagnosis of HNC [13] Patients were separated into three

categories: those without hyperlipidemia (nH) (n = 495, 31.0%), those with hyperlipidemia and not taking a statin (HnS) (n = 567, 35.6%) and those with hyperlipidemia and taking a statin (H + S) (n = 530, 33.3%). Hyperlipidemia was determined using ICD-9 diagnosis codes as well.

Our two primary outcomes included two year OS and two year cancer specific survival (CSS). Medicare longitudinal data provided

Table 2B
Cancer specific survival.

		Univariate Kaplan-Meier			Univariate cox PH			Multivariate cox PH			
		CSS2	95% CI	p	HR	95% CI	p	HR	95% CI	p (class)	p (variable)
Hyperlipidemia/statins category	H + S	81.2%	76.6–85%	< 0.01	0.04
	nH	69.1%	63.6–73.9%	.	1.77	1.29–2.41	< 0.01	1.56	1.1–2.21	0.01	.
	HnS	69.2%	64–73.8%	.	1.70	1.25–2.31	< 0.01	1.37	0.99–1.89	0.06	.
5-year age categories	66–69	76.8%	71.1–81.6%	< 0.01	< 0.01
	70–74	78.5%	73.3–82.8%	.	0.94	0.66–1.33	0.71	1.01	0.7–1.46	0.96	.
	75 and older	67.9%	63.3–72%	.	1.49	1.11–2.01	< 0.01	1.69	1.23–2.33	< 0.01	.
Sex	Male	76.4%	72.6–79.7%	0.01	< 0.01
	Female	69.0%	64.3–73.2%	.	1.35	1.06–1.71	0.01	1.48	1.13–1.94	< 0.01	.
Race/ethnicity	White NH	75.1%	71.9–77.9%	0.03	0.15
	Non-white or hispanic	65.7%	58.4–72%	.	1.36	1.03–1.78	0.03	0.64	0.35–1.17	0.15	.
Marital status	Married or partnered	79.5%	75.5–82.9%	< 0.01	0.16
	Non-married	67.8%	63.6–71.6%	.	1.66	1.29–2.12	< 0.01	1.21	0.92–1.59	0.16	.
Geographic region	West	70.6%	66–74.7%	0.06	0.08
	East	75.7%	68.7–81.4%	.	0.80	0.57–1.13	0.2	0.66	0.44–0.99	0.04	.
	Midwest	83.1%	75.2–88.7%	.	0.58	0.36–0.91	0.02	0.56	0.33–0.95	0.03	.
	South	71.3%	65.4–76.4%	.	1.02	0.77–1.35	0.9	0.75	0.53–1.06	0.10	.
Patient location	Metropolitan	73.7%	70.4–76.6%	0.35	0.87
	Non-Metropolitan	71.4%	64.7–77%	.	1.14	0.86–1.52	0.36	0.97	0.69–1.37	0.87	.
Year of diagnosis	2008	74.2%	69.2–78.5%	0.80	0.79
	2009	72.2%	67.2–76.5%	.	1.10	0.83–1.46	0.51	1.11	0.83–1.48	0.50	.
	2010	73.6%	67.3–79%	.	1.04	0.77–1.41	0.79	1.07	0.79–1.46	0.65	.
Primary site ¹	Oral cavity	77.1%	73.1–80.5%	< 0.01	0.01
	Oropharynx	70.7%	65.6–75.3%	.	1.39	1.07–1.81	0.01	0.61	0.44–0.85	< 0.01	.
	Other	65.3%	56.9–72.5%	.	1.70	1.23–2.36	< 0.01	0.71	0.49–1.03	0.07	.
Tumor size stage	T0-1	88.8%	84.6–91.8%	< 0.01	< 0.01
	T2	70.7%	64.8–75.8%	.	2.78	1.87–4.12	< 0.01	1.73	0.68–4.42	0.25	.
	T3-4	56.3%	50.1–62.1%	.	5.24	3.59–7.63	< 0.01	7.47	3.08–18.12	< 0.01	.
	Unknown	74.7%	66.5–81.2%	.	2.69	1.69–4.29	< 0.01	5.37	1.95–14.73	< 0.01	.
Nodal stage	N0	81.2%	77.7–84.2%	< 0.01	< 0.01
	N1	64.0%	56–70.9%	.	2.13	1.56–2.91	< 0.01	1.58	1.11–2.25	0.01	.
	N2-3	62.4%	56.3–67.9%	.	2.24	1.71–2.93	< 0.01	1.81	1.3–2.51	< 0.01	.
Comorbidity index	< 0.01	76.1%	72.6–79.2%	< 0.01	0.04
	1 or more	68.0%	62.9–72.7%	.	1.47	1.16–1.87	< 0.01	1.32	1.02–1.71	0.04	.
Most-visited facility was teaching hospital	No or unknown	69.4%	65–73.4%	0.01	0.14
	Yes	76.4%	72.5–79.8%	.	0.72	0.56–0.91	< 0.01	0.83	0.64–1.07	0.14	.
Tract pct high school only - above median	Not above median	76.4%	72.3–80%	< 0.01	< 0.01
	Above median	70.0%	65.8–73.8%	.	1.42	1.12–1.8	< 0.01	1.64	1.2–2.23	< 0.01	.
Tract pct below poverty - above median	Not above median	78.6%	74.7–82%	< 0.01	0.36
	Above median	67.9%	63.5–71.8%	.	1.64	1.29–2.09	< 0.01	1.15	0.86–1.54	0.36	.
Surgery	No	59.0%	54–63.7%	< 0.01	< 0.01
	Yes	83.0%	79.7–85.8%	.	0.34	0.27–0.44	< 0.01	0.22	0.11–0.42	< 0.01	.
Chemotherapy	No	80.6%	77–83.7%	< 0.01	0.85
	Yes	64.6%	59.9–68.8%	.	1.92	1.51–2.45	< 0.01	1.03	0.75–1.42	0.85	.
Radiation therapy	No radiation	85.7%	81.6–88.9%	< 0.01	< 0.01
	Radiation	66.4%	62.5–69.9%	.	2.52	1.87–3.41	< 0.01	0.34	0.16–0.7	< 0.01	.
Metformin	No	71.9%	68.9–74.7%	< 0.01	< 0.01
	Yes	88.5%	78.8–93.9%	.	0.37	0.19–0.72	< 0.01	0.39	0.19–0.79	< 0.01	.
Hypertension	No	75.5%	69.6–80.5%	0.34	0.26
	Yes	72.4%	69–75.5%	.	1.15	0.86–1.53	0.34	1.21	0.87–1.7	0.26	.
Diabetes	No	73.6%	70.2–76.8%	0.57	0.14
	Yes	72.2%	66.7–76.9%	.	1.08	0.83–1.39	0.58	1.24	0.93–1.65	0.14	.

Other sites include hypopharynx, nasopharynx, pyriform sinus, salivary glands.

Legend: CSS2, percent 2-year cancer-specific survival; 95% CI, 95% confidence intervals; PH, proportional hazard; HR, hazard ratio.

more information about death in patients; therefore, this dataset was used for capturing OS. Only the SEER dataset included CSS data. It excluded patients that died from causes other than cancer. SEER patients who were diagnosed in 2011 were also excluded due to limited time for follow-up.

Our secondary outcome was cancer-related toxicity experienced within 6 months of initiating definitive therapy. Cancer-related toxicity-related events included weight loss, antiemetic use, emergency department visit, hospital/ED visit with nausea/emesis/diarrhea, hospital/ED visit with dehydration, hospital/ED visit with malnutrition, gastrostomy or feeding tube placement, dysphagia, acute renal failure, aspiration pneumonia, tracheostomy or airway obstruction,

pneumonia, speech pathology, and hospital/ED visit with neutropenia/thrombocytopenia. These events were identified using claim procedures and diagnosis codes. Statin-associated toxicities including myositis and transaminitis were not collected.

Control variables in multivariate analysis

In multivariate analysis of the SEER data of HNC patients, we controlled for age, sex, race/ethnicity, marital status, geographic region (West, East, Midwest, South), patient location (metropolitan, non-metropolitan), year of diagnosis, primary site (oral cavity, oropharynx, or other) AJCC T stage, N stage, comorbidity index (CCI), whether the

patient was treated at a teaching hospital, census tract percentage of the population with high school education only, census tract percentage of the population below poverty, surgery, chemotherapy, radiotherapy, metformin use, hypertension, and diabetes. The Charleston Comorbidity Index (CCI) from the National Cancer institute [14] was used to adjust for overall health.

We also performed a stratified analysis of each type of HNC (oral cavity, oropharynx, and other, which includes hypopharynx, nasopharynx, pyriform sinus, and salivary glands) to explore the effect of statins based on subsite. We controlled for the same variables as above, minus HNC location for this analysis.

Statistical analysis

All analyses were done in SAS 9.4 (SAS Institute Inc., Cary, NC).

Patient characteristics

Univariate associations in categorical patient characteristic variables and hyperlipidemia/statin groups were determined using Pearson chi-square methodology.

Survival

OS and CSS were first analyzed through Kaplan-Meier analysis for each subsite. Then, an unadjusted Cox proportional hazard model was utilized to calculate hazard ratios (HR) with 95% confidence intervals for univariate and multivariate analyses. Regression analysis was done to calculate both OS and CSS, with a significance limit of $p < 0.05$. A test of Schoenfeld residuals for covariates in all models was used to determine proportional hazard assumption, and no results were significant [15].

Results

Patient characteristics

In total, there were 1592 patients included in this study. 495 were in the nH group, 567 were in the HnS group, and 530 were in the H + S group. Most patients were older than 70, male, white non-hispanic, non-married, lived in a metropolitan area, and had a primary cancer in the oral cavity. Most patients also had NO disease, a CCI of 0, were treated at a teaching hospital, had above a high school education, lived below the poverty line, received surgery and radiation but not chemotherapy, and had hypertension but did not have diabetes (Table 1).

Overall survival outcomes

The H + S group displayed the highest OS at 2 years (73.0%, 95% CI 69.0, 76.6%), while the nH and HnS groups had significantly lower OS (58.6%, 95% CI 54.1, 62.8%; 61.7%, 95% CI 57.6, 65.6% respectively, $p < 0.01$) (Table 2A). CSS demonstrated similar trends, with H + S having significantly higher CSS (81.2%, 95% CI 76.6, 85.0%) than both nH (69.1%, 95% CI 63.6, 73.9%) and HnS (69.2%, 95% CI 64.0, 73.8%) ($p < 0.01$) (Table 2B). Figs. 2A and 2B display the Kaplan-Meier curves for OS and CSS, respectively.

Predictors of OS and CSS

Both nH (HR = 1.64, 95% CI 1.29, 2.07) and HnS (HR = 1.40, 95% CI 1.12, 1.74) had worse OS at 2 years compared to H + S according to

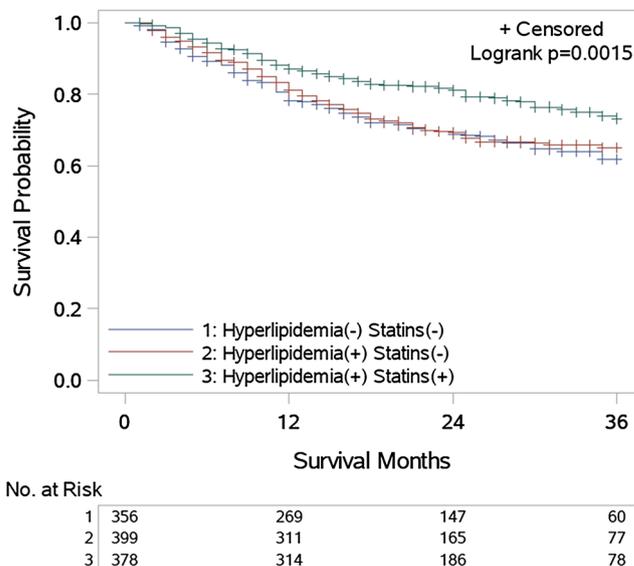


Fig. 2A. Kaplan-Meier curve of 3 year overall survival.

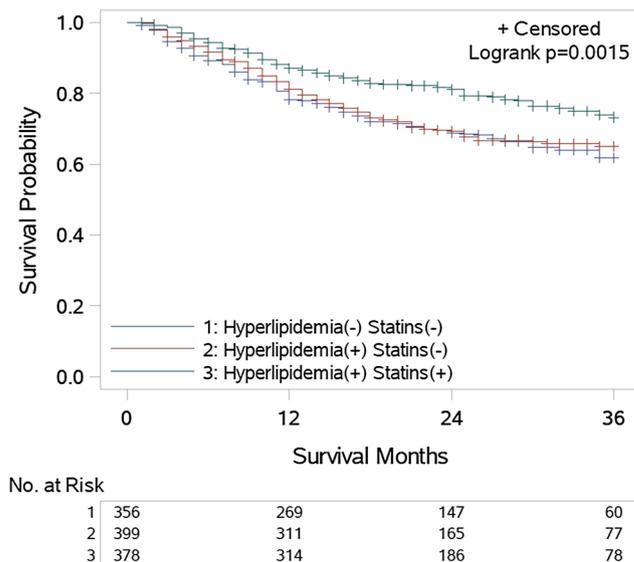


Fig. 2B. Kaplan-Meier curve of 3 year cancer specific survival.

multivariate Cox proportional hazard regression ($p < 0.01$). Younger age, being married, lower T and N stage, lower CCI score, being treated at a university hospital, below a high school education level, and receiving surgery and radiation were associated with higher OS. Patients who had a primary cancer from the oral cavity had a lower OS (Table 2A).

In multivariate analysis of CSS, H + S had better CSS at 2 years compared to both nH (HR = 1.56, 95% CI 1.1, 2.21) and H + S (HR = 1.37, 95% CI 0.99, 1.89) ($p = 0.04$). Patients that were younger, male, had a lower T and N stage, had a lower CCI score, did not have a above a high school education, received chemotherapy, radiation, and metformin also had higher CSS. Patients who had a primary cancer from the oral cavity had lower CSS (Table 2B).

Table 3A
Overall survival (oral cavity).

		Univariate Kaplan-Meier			Univariate cox PH			Multivariate cox PH			
		OSS2	95% CI	p	HR	95% CI	p	HR	95% CI	p (class)	p (variable)
Hyperlipidemia/statins category	H + S	77.7%	72.4–82.2%	< 0.0001	< 0.01
	nH	61.9%	55.5–67.7%		1.9	1.38–2.62	< 0.0001	1.47	1.05–2.05	0.03	.
	HnS	63.5%	57.6–68.9%		1.78	1.3–2.43	< 0.01	1.83	1.28–2.61	< 0.01	.
5-year age categories	66–69	72.1%	64.3–78.5%	< 0.0001	< 0.0001
	70–74	81.3%	75.3–85.9%		0.64	0.42–0.99	0.05	0.7	0.45–1.1	0.13	.
	75 and older	60.4%	55.7–64.8%		1.56	1.12–2.18	0.01	1.76	1.23–2.52	< 0.01	.
Sex	Male	69.2%	64.3–73.6%	0.41	0.57
	Female	67.0%	62.3–71.2%		1.11	0.87–1.42	0.41	0.92	0.7–1.22	0.57	.
Race/ethnicity	White NH	69.6%	65.9–72.9%	0.06	0.96
	Non-white or hispanic	61.3%	53.1–68.6%		1.32	0.99–1.77	0.06	0.99	0.71–1.39	0.96	.
Marital status	Married or partnered	74.0%	69.2–78.2%	< 0.01	0.06
	Non-married	63.0%	58.3–67.3%		1.54	1.2–1.99	< 0.01	1.31	0.99–1.73	0.06	.
Geographic region	West	67.0%	61.6–71.8%	0.03	0.13
	East	71.3%	62.9–78.2%		0.85	0.59–1.23	0.39	0.69	0.44–1.06	0.09	.
	Midwest	77.4%	69–83.8%		0.66	0.43–0.99	0.05	0.78	0.48–1.26	0.31	.
	South	62.2%	55.4–68.3%		1.21	0.91–1.61	0.20	1.09	0.75–1.57	0.66	.
Patient location	Metropolitan	68.1%	64.2–71.6%	0.93	0.9
	Non-metropolitan	67.6%	61.1–74%		1.01	0.76–1.34	0.93	1.02	0.72–1.46	0.9	.
Year of diagnosis	2008	70.4%	60.4–73.7%	0.65	0.95
	2009	69.5%	63.5–76.3%		0.9	0.63–1.29	0.57	0.95	0.66–1.38	0.79	.
	2010	65.2%	62.4–75.6%		0.94	0.65–1.35	0.72	1.06	0.73–1.55	0.77	.
Tumor size stage	T0-1	83.3%	78.8–87%	< 0.0001	< 0.0001
	T2	61.6%	54.5–68%		2.64	1.86–3.75	< 0.0001	3.54	1.45–8.65	0.01	.
	T3-4	46.7%	39.2–53.8%		4.37	3.12–6.12	< 0.0001	10.33	4.26–25.03	< 0.0001	.
	Unknown	70.4%	60.8–78%		2.02	1.3–3.14	< 0.001	5.66	2.05–15.62	< 0.01	.
Nodal stage	N0	76.1%	72.5–79.3%	< 0.0001	< 0.0001
	N1	49.4%	38.7–59.3%		2.5	1.79–3.49	< 0.0001	1.58	1.07–2.31	0.02	.
	N2-3	37.1%	28–46.3%		3.52	2.63–4.71	< 0.0001	2.76	1.91–3.99	< 0.0001	.
Comorbidity index	< 0.01	73.0%	69–76.6%	< 0.0001	< 0.01
	1 or more	58.9%	52.9–64.4%		1.71	1.34–2.18	< 0.0001	1.64	1.25–2.15	< 0.01	.
Most-visited facility was teaching hospital	No or unknown	64.6%	59.3–69.3%	0.07	0.33
	Yes	70.7%	66.3–74.7%		0.8	0.62–1.02	0.07	0.88	0.67–1.15	0.33	.
Tract pct high school only - above median	Not above median	67.6%	62.5–72.1%	0.9	0.63
	Above median	68.4%	63.8–72.6%		0.99	0.77–1.26	0.9	0.92	0.67–1.28	0.63	.
Tract pct below poverty - above median	Not above median	73.2%	68.6–77.3%	< 0.01	0.51
	Above median	63.0%	58.1–67.5%		1.48	1.16–1.9	< 0.01	1.1	0.83–1.47	0.51	.
Surgery	No	38.6%	30.4–46.8%	< 0.0001	< 0.01
	Yes	73.8%	70.3–77%		0.32	0.24–0.41	< 0.0001	0.28	0.14–0.54	< 0.01	.
Chemotherapy	No	73.8%	70.2–77%	< 0.0001	0.18
	Yes	47.4%	39.9–54.6%		2.36	1.83–3.05	< 0.0001	1.26	0.9–1.77	0.18	.
Radiation therapy	No radiation	78.4%	74.4–81.8%	< 0.0001	< 0.01
	Radiation	53.7%	48.2–58.9%		2.45	1.91–3.15	< 0.0001	0.25	0.12–0.51	< 0.01	.
Metformin	No	67.7%	64.2–70.9%	0.4	0.58
	Yes	72.1%	59.8–81.2%		0.82	0.51–1.31	0.4	0.86	0.5–1.48	0.58	.
Hypertension	No	70.5%	63.1–76.6%	0.32	0.03
	Yes	67.4%	63.5–70.9%		1.17	0.86–1.58	0.33	1.49	1.04–2.14	0.03	.
Diabetes	No	68.4%	64.4–72.1%	0.71	0.68
	Yes	67.1%	60.8–72.6%		1.05	0.81–1.37	0.71	1.07	0.78–1.47	0.68	.

Legend: OSS2, percent 2-year overall survival; 95% CI, 95% confidence intervals; PH, proportional hazard; HR, hazard ratio.

Predictors of OS and CSS based on subsite

Multivariate analysis of OS based on subsite displayed similar trends; H + S demonstrated improved OS compared to nH (HR = 1.47, 95% CI 1.05, 2.05) and HnS (HR = 1.83, 95% CI 1.28, 2.61) in HNC patients with primary disease in the oral cavity (p < 0.01) (Table 3A). OS was also higher in H + S patients with oropharyngeal disease compared to nH (HR = 1.51, 95% CI 1.03, 2.21) and HnS (HR = 1.65, 95% CI 1.08, 2.5) patients (p = 0.05) (Table 4A).

In addition, H + S patients with disease in the oral cavity also had a trend towards improved CSS compared to nH (HR = 1.18, 95% CI 0.7, 1.99) and HnS (HR = 1.62, 95% CI 0.94, 2.81) patients (p = 0.20) (Table 3B). Those with primary disease in the oropharynx similarly displayed trends towards improved CSS vs. nH (HR = 1.64, 95% CI 0.93, 2.87) and HnS (HR = 1.68, 95% CI 0.9, 3.14) patients (p = 0.19) (Table 4B).

“Other” primary sites (which include hypopharynx, nasopharynx, pyriform sinus, and salivary glands) had improved OS in nH

Table 3B
Cancer specific survival (oral cavity).

		Univariate Kaplan-Meier			Univariate Cox PH			Multivariate Cox PH			
		CSS2	95% CI	p	HR	95% CI	p	HR	95% CI	p (class)	p (variable)
Hyperlipidemia/statins category	H + S	84.8%	78.5–89.4%	0.01	0.20
	nH	73.4%	65.7–79.6%		1.93	1.19–3.12	< 0.01	1.18	0.7–1.99	0.52	.
	HnS	72.5%	65.1–78.6%		1.93	1.2–3.09	< 0.01	1.62	0.94–2.81	0.09	.
5-year age categories	66–69	75.3%	65.5–82.7%	0.07	0.06
	70–74	84.1%	76.9–89.2%		0.65	0.37–1.15	0.14	0.68	0.37–1.26	0.22	.
	75 and older	74.1%	68.2–79%		1.13	0.71–1.78	0.61	1.26	0.75–2.12	0.37	.
Sex	Male	79.5%	73.7–84.1%	0.19	0.16
	Female	74.9%	69.2–79.8%		1.27	0.88–1.84	0.19	1.36	0.88–2.1	0.16	.
Race/ethnicity	White NH	79.8%	75.6–83.4%	< 0.01	0.22
	Non-white or Hispanic	65.0%	54.1–73.8%		1.79	1.2–2.67	< 0.01	1.38	0.83–2.29	0.22	.
	Married	82.5%	77.1–86.8%	0.01	0.43
Marital status	Non-married	72.4%	66.5–77.4%		1.63	1.12–2.38	0.01	1.20	0.77–1.87	0.43	.
	Geographic region	West	72.8%	66.1–78.3%	0.06	0.29
Patient location	East	80.3%	70–87.4%		0.69	0.4–1.19	0.18	0.57	0.29–1.1	0.09	.
	Midwest	88.2%	78.5–93.7%		0.42	0.21–0.85	0.02	0.56	0.25–1.28	0.17	.
	South	75.7%	67.4–82.1%		0.95	0.62–1.45	0.79	0.73	0.42–1.28	0.27	.
	Metropolitan	77.5%	72.9–81.4%	0.49	0.39
Year of diagnosis	Non-metropolitan	75.6%	67.1–82.2%		1.15	0.77–1.74	0.50	1.27	0.74–2.19	0.39	.
	2008	77.6%	70.6–83.1%	0.94	0.51
Tumor size stage	2009	76.9%	70.3–82.3%		1.07	0.69–1.64	0.77	1.18	0.75–1.85	0.48	.
	2010	75.0%	62.4–84%		1.07	0.68–1.7	0.77	1.34	0.82–2.19	0.25	.
	T0-1	90.0%	85.2–93.3%	< 0.0001	< 0.01
Nodal stage	T2	68.6%	58.7–76.7%		3.40	1.99–5.8	< 0.0001	2.16	0.55–8.47	0.27	.
	T3-4	56.9%	46.6–65.9%		6.02	3.61–10.05	< 0.0001	10.41	2.73–39.7	< 0.01	.
	Unknown	77.5%	65.4–85.8%		2.63	1.38–5.01	< 0.01	9.07	2.05–40.15	< 0.01	.
	N0	85.9%	82.1–89%	< 0.0001	< 0.01
Comorbidity index	N1	48.0%	32.1–62.3%		4.54	2.85–7.24	< 0.0001	2.47	1.43–4.28	< 0.01	.
	N2-3	45.4%	32.9–57%		4.91	3.23–7.47	< 0.0001	2.88	1.69–4.9	< 0.0001	.
Most-visited facility was teaching hospital	< 0.01	79.7%	75–83.6%	0.04	0.42
	1 or more	71.7%	64–78.1%		1.48	1.02–2.13	0.04	1.19	0.79–1.79	0.42	.
Tract pct high school only - above median	No or unknown	72.3%	65.9–77.7%	0.02	0.28
	Yes	80.8%	75.6–85%		0.65	0.45–0.93	0.02	0.80	0.53–1.2	0.28	.
Tract pct below poverty - above median	Not above median	77.9%	71.8–82.8%	0.34	0.47
	Above median	76.4%	70.9–80.9%		1.19	0.83–1.72	0.34	1.19	0.74–1.9	0.47	.
Surgery	Not above median	84.6%	79.4–88.6%	< 0.0001	0.09
	Above median	69.5%	63.4–74.8%		2.26	1.54–3.31	< 0.0001	1.48	0.94–2.33	0.09	.
Chemotherapy	No	41.2%	29.7–52.2%	< 0.0001	< 0.01
	Yes	83.7%	79.8–86.9%		0.19	0.13–0.28	< 0.0001	0.40	0.24–0.66	< 0.01	.
Radiation therapy	No	85.0%	81.1–88.2%	< 0.0001	0.10
	Yes	48.7%	38.8–57.9%		4.03	2.8–5.78	< 0.0001	1.49	0.92–2.41	0.10	.
Metformin	No radiation	89.6%	85.6–92.6%	< 0.0001	0.14
	Radiation	58.6%	51.3–65.1%		4.62	3.08–6.94	< 0.0001	0.47	0.17–1.29	0.14	.
Hypertension	No	76.0%	71.7–79.6%	0.08	0.10
	Yes	88.7%	76.5–94.7%		0.49	0.21–1.1	0.08	0.45	0.18–1.15	0.10	.
Diabetes	No	77.0%	72.3–81.1%	0.94	0.02
	Yes	77.2%	69.4–83.2%		0.99	0.66–1.47	0.94	1.94	1.1–3.42	0.02	.
	No	80.5%	72–86.6%	0.32	0.68
	Yes	76.1%	71.4–80%		1.26	0.8–1.98	0.33	1.11	0.69–1.76	0.68	.

Legend: CSS2, percent 2-year cancer-specific survival; 95% CI, 95% confidence intervals; PH, proportional hazard; HR, hazard ratio.

(HR = 0.86, 95% CI 0.48, 1.53) patients vs. H + S and HnS (HR = 1.28, 95% CI 0.69, 2.37) patients and improved CSS in HnS (HR = 0.88, 95% CI 0.35, 2.19) patients vs. H + S and nH (HR = 1.06, 95% CI 0.46, 2.46) patients, although neither was statistically significant (p = 0.46 and 0.91, respectively) (Tables 5A and 5B).

Toxicity

Common cancer-related toxicity-related events among all three groups included weight loss (n = 552, 34.7%), antiemetic use (n = 750, 47.1%), gastrostomy or feeding tube use (n = 613, 38.5%),

and dysphagia (n = 758, 47.6%). Fewer H + S patients used antiemetics compared to HnS patients (p = 0.03). There were no other significant differences in the incidence of cancer-related toxicity-related events between the three groups (Table 6).

Discussion

To our knowledge this is the first published report to correlate statin use and hyperlipidemia with cancer specific and overall mortality in HNC patients in multiple subsites (oral cavity, oropharynx and other). Using longitudinal HNC data from both SEER and Medicare databases,

Table 4A
Overall survival (oropharynx).

		Univariate Kaplan-Meier			Univariate Cox PH			Multivariate Cox PH			
		CSS2	95% CI	p	HR	95% CI	p	HR	95% CI	p (class)	p (variable)
Hyperlipidemia/statins category	H + S	73.0%	65.7–79%	< 0.01	0.05
	nH	57.0%	49.4–63.9%		1.78	1.24–2.56	< 0.01	1.51	1.03–2.21	0.04	.
	HnS	59.2%	52.3–65.4%		1.67	1.17–2.37	< 0.01	1.65	1.08–2.5	0.02	.
5-year age categories	66–69	75.5%	68.7–81.1%	< 0.0001	< 0.0001
	70–74	67.2%	59.8–73.6%		1.46	0.99–2.14	0.06	1.47	0.98–2.2	0.06	.
	75 and older	46.8%	39.8–53.5%		2.78	1.97–3.92	< 0.0001	2.59	1.79–3.75	< 0.0001	.
Sex	Male	66.0%	61.2–70.4%	0.01	0.51
	Female	54.5%	46.6–61.8%		1.43	1.08–1.89	0.01	1.12	0.81–1.54	0.51	.
Race/ethnicity	White NH	64.5%	59.9–68.7%	0.07	0.73
	Non-white or Hispanic	55.6%	46.1–64%		1.33	0.97–1.82	0.07	1.06	0.75–1.51	0.73	.
Marital status	Married or Partnered	71.6%	65.8–76.7%	< 0.0001	0.01
	Non-married	55.2%	49.4–60.5%		1.8	1.36–2.38	< 0.0001	1.55	1.12–2.13	0.01	.
Geographic region	West	59.1%	52.7–64.9%	0.4	0.03
	East	68.4%	58.2–76.6%		0.74	0.49–1.1	0.13	0.6	0.38–0.97	0.04	.
	Midwest	63.8%	50.1–74.7%		0.85	0.53–1.35	0.49	0.63	0.36–1.11	0.11	.
	South	64.3%	56.5–71%		0.83	0.6–1.14	0.25	0.59	0.4–0.86	0.01	.
Patient location	Metropolitan	63.5%	59–67.6%	0.33	0.98
	Non-Metropolitan	59.0%	48.7–67.9%		1.18	0.84–1.66	0.34	0.99	0.67–1.47	0.98	.
Year of diagnosis	2008	61.5%	52.6–69.3%	0.07	0.2
	2009	54.5%	45.3–62.9%		1.17	0.8–1.71	0.43	1.22	0.81–1.83	0.34	.
	2010	61.5%	53–69%		0.97	0.66–1.42	0.87	1.11	0.75–1.65	0.6	.
Tumor size stage	T0-1	73.9%	64.6–81%	< 0.0001	0.01
	T2	66.0%	59–72.1%		1.31	0.85–2.02	0.22	1.17	0.73–1.86	0.52	.
	T3-4	49.4%	42–56.5%		2.34	1.54–3.56	< 0.0001	1.83	1.15–2.92	0.01	.
	Unknown	68.8%	57.4–77.7%		1.29	0.75–2.2	0.36	1.13	0.64–2.01	0.68	.
Nodal stage	N0	63.8%	56.4–70.2%	0.39	0.06
	N1	57.5%	48.4–65.5%		1.22	0.85–1.75	0.27	1.59	1.08–2.35	0.02	.
	N2-3	64.5%	58.3–70%		0.98	0.72–1.34	0.90	1.35	0.94–1.94	0.1	.
Comorbidity index	< 0.01	68.1%	62.9–72.7%	< 0.01	< 0.01
	1 or more	53.9%	47.1–60.3%		1.67	1.28–2.19	< 0.01	1.61	1.2–2.16	< 0.01	.
Most-visited facility was teaching hospital	No or unknown	59.0%	52.9–64.7%	0.06	0.06
	Yes	65.9%	60.3–70.9%		0.77	0.59–1.01	0.06	0.76	0.56–1.02	0.06	.
Tract pct high school only - above median	Not above Median	67.6%	61.9–72.6%	0.01	< 0.01
	Above median	57.5%	51.4–63%		1.42	1.08–1.86	0.01	1.81	1.28–2.57	< 0.01	.
Tract pct below poverty - above median	Not above Median	66.2%	60.5–71.3%	0.05	0.97
	Above median	59.0%	53–64.5%		1.3	1–1.71	0.05	0.99	0.71–1.39	0.97	.
Surgery	No	57.7%	52.7–62.5%	< 0.01	0.03
	Yes	73.2%	66.2–79%		0.58	0.42–0.8	< 0.01	0.65	0.44–0.95	0.03	.
Chemotherapy	No	58.2%	50.1–65.5%	0.12	0.2
	Yes	64.4%	59.6–68.8%		0.8	0.6–1.06	0.12	0.79	0.55–1.13	0.2	.
Radiation therapy	No radiation	58.2%	45.5–68.9%	0.16	< 0.0001
	Radiation	63.3%	58.9–67.3%		0.76	0.51–1.12	0.17	0.18	0.08–0.4	< 0.0001	.
Metformin	No	61.9%	57.6–65.9%	0.11	0.14
	Yes	75.8%	57.3–87.1%		0.57	0.28–1.16	0.12	0.56	0.26–1.2	0.14	.
Hypertension	No	67.8%	59.6–74.7%	0.12	0.9
	Yes	60.9%	56.1–65.4%		1.29	0.93–1.78	0.12	1.02	0.71–1.49	0.9	.
Diabetes	No	66.5%	61.6–70.9%	0.01	< 0.01
	Yes	54.4%	46.9–61.4%		1.45	1.1–1.92	0.01	1.67	1.22–2.28	< 0.01	.

Legend: OS2, percent 2-year overall survival; 95% CI, 95% confidence intervals; PH, proportional hazard; HR, hazard ratio.

we demonstrate improved OS and CSS in H + S patients with primary disease in the oral cavity and oropharynx compared to both nH and HnS patients, even after adjusting for covariates in multivariate regression. This, we also show, did not come at a cost of excess toxicity-related events.

Stratified analysis of survival outcomes based on subsite was performed because adjusted analysis demonstrated worse survival in HNC patients with oral cavity disease compared to those with oropharynx and other (hypopharynx, nasopharynx, pyriform sinus, and salivary glands) disease, while unadjusted analysis showed the opposite (Tables

2A and 2B). This is most likely due to the fact that oral cavity disease was diagnosed at an earlier stage and treated more aggressively, therefore univariate analysis falsely demonstrated improved OS and CSS. However, stratified multivariate analysis based on subsite still showed improved survival outcomes in H + S patients with oral cavity and oropharynx disease compared to nH and HnS patients.

Improved outcomes in the H + S group compared to the HnS group supports the use of statins in cancer patients with similar comorbidities. This may be a reflection of patient compliance to treatment and avoidance of unhealthy behaviors. However, H + S patients also

Table 4B
Cancer specific survival (oropharynx).

		Univariate Kaplan-Meier			Univariate Cox PH			Multivariate Cox PH			
		CSS2	95% CI	p	HR	95% CI	p	HR	95% CI	p (class)	p (variable)
Hyperlipidemia/statins category	H + S	82.6%	74.2–88.5%	0.01	0.19
	nH	65.8%	55.9–73.9%		2.18	1.27–3.74	< 0.01	1.64	0.93–2.87	0.09	.
	HnS	64.6%	55.4–72.4%		2.18	1.29–3.68	< 0.01	1.68	0.9–3.14	0.1	.
5-year age categories	66–69	80.1%	71.7–86.3%	< 0.01	0.02
	70–74	73.3%	63.9–80.6%		1.39	0.82–2.38	0.23	1.43	0.8–2.56	0.23	.
	75 and older	59.1%	49.4–67.6%		2.36	1.45–3.85	< 0.01	2.15	1.26–3.67	0.01	.
Sex	Male	76.8%	70.8–81.7%	< 0.01	0.01
	Female	58.8%	49–67.4%		1.86	1.26–2.73	< 0.01	1.8	1.15–2.82	0.01	.
Race/ethnicity	White NH	73.1%	67.5–78%	0.08	0.58
	Non-white or Hispanic	61.8%	49.3–72.1%		1.47	0.95–2.26	0.08	1.16	0.69–1.93	0.58	.
	Marital status	Married or Partnered	77.7%	70.4–83.5%	< 0.01
Geographic region	Non-married	65.0%	57.6–71.4%		1.69	1.13–2.53	0.01	1.32	0.83–2.09	0.25	.
	West	66.1%	57.8–73.2%	0.37	0.02
	East	76.8%	64.8–85.2%		0.63	0.36–1.11	0.11	0.47	0.24–0.93	0.03	.
Patient location	Midwest	74.9%	55.4–86.8%		0.73	0.35–1.53	0.40	0.34	0.13–0.88	0.03	.
	South	72.4%	62.5–80.2%		0.81	0.51–1.29	0.37	0.46	0.26–0.81	0.01	.
	Metropolitan	71.9%	66.2–76.8%	0.35	0.69
Year of diagnosis	Non-Metropolitan	65.5%	52.1–76%		1.25	0.78–2	0.35	1.12	0.64–1.94	0.69	.
	2008	73.2%	64.3–80.1%	0.82	0.84
	2009	68.1%	58.5–75.9%		1.16	0.72–1.86	0.54	1.02	0.61–1.7	0.93	.
Tumor size stage	2010	72.2%	63.1–79.4%		1.05	0.65–1.7	0.83	1.15	0.7–1.9	0.58	.
	T0-1	88.1%	77.2–94%	< 0.0001	0.01
	T2	71.8%	62.5–79.3%		2.46	1.13–5.32	0.02	2.34	1.02–5.35	0.04	.
Nodal stage	T3-4	55.8%	45.8–64.7%		4.88	2.31–10.31	< 0.0001	3.64	1.59–8.33	0	.
	Unknown	75.4%	61.8–84.7%		2.46	1.03–5.85	0.04	2.02	0.8–5.12	0.14	.
	N0	69.3%	59.4–77.2%	0.88	0.73
Comorbidity index	N1	68.7%	57.2–77.7%		1.05	0.63–1.74	0.86	1.25	0.7–2.2	0.45	.
	N2-3	72.7%	65–79%		0.93	0.59–1.45	0.74	1.18	0.69–2	0.54	.
	< 0.01	71.9%	65.3–77.4%	0.31	0.54
Most-visited facility was Teaching Hospital	1 or more	69.4%	60.8–76.6%		1.22	0.83–1.81	0.32	1.15	0.75–1.76	0.54	.
	No or Unknown	66.8%	59–73.4%	0.06	0.13
Tract pct high school only - Above Median	Yes	74.4%	67.2–80.2%		0.7	0.47–1.03	0.07	0.71	0.46–1.11	0.13	.
	Not above Median	77.2%	70.2–82.8%	< 0.01	< 0.01
Tract pct below poverty - Above Median	Above median	63.7%	55.9–70.5%		1.77	1.19–2.63	< 0.01	2.52	1.51–4.2	< 0.01	.
	Not above Median	75.1%	67.8–81%	0.06	0.94
Surgery	Above median	66.6%	59–73.1%		1.45	0.98–2.15	0.06	0.98	0.6–1.62	0.94	.
	No	65.1%	58.5–70.8%	< 0.01	0.03
Chemotherapy	Yes	82.9%	74.4–88.8%		0.45	0.27–0.74	< 0.01	0.5	0.27–0.92	0.03	.
	No	69.6%	58.6–78.2%	0.75	0.91
Radiation therapy	Yes	71.2%	65.2–76.3%		0.93	0.6–1.44	0.75	1.03	0.6–1.77	0.91	.
	No radiation	61.8%	43.3–75.9%	0.08	0.01
Metformin	Radiation	71.8%	66.4–76.5%		0.62	0.36–1.07	0.09	0.4	0.21–0.76	0.01	.
	No	69.8%	64.4–74.5%	0.07	0.08
Hypertension	Yes	85.9%	51.1–96.6%		0.3	0.07–1.21	0.09	0.26	0.06–1.17	0.08	.
	No	74.3%	64–82.1%	0.42	0.8
Diabetes	Yes	69.4%	63.2–74.7%		1.21	0.76–1.9	0.42	0.93	0.54–1.61	0.8	.
	No	74.0%	67.9–79.2%	0.08	0.01
	Yes	64.1%	54.2–72.3%		1.42	0.96–2.1	0.08	1.91	1.21–3.01	0.01	.

Legend: CSS2, percent 2-year cancer-specific survival; 95% CI, 95% confidence intervals; PH, proportional hazard; HR, hazard ratio.

showed improved OS and CSS when compared to nH patients. Therefore, it is possible that statins disrupt cancer cell metabolism and proliferation.

Statins inhibit the rate-limiting enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase in the cholesterol synthesis pathway [7], which impacts cell membrane integrity, protein synthesis, cell signaling, and cell cycle progression [16]. Independent of lowering cholesterol levels, statins have also been reported to decrease proliferation,

promote apoptosis in neoplastic cells [17], and prevent cancer cell invasion [18,19]. Their potential role as chemo- or radio-sensitizers has been reported in different cancer subtypes [16,20,21]. These findings are particularly relevant in HNC, where radiotherapy (and chemotherapy) represent a cornerstone treatment for this disease [22].

The ability of statins to improve survival did not come at a cost of increasing cancer-related toxicity events; in fact, anti-emetic use was significantly lower in the H + S patients compared to HnS. Although

Table 5A
Overall survival (other*).

		Univariate Kaplan-Meier			Univariate Cox PH			Multivariate Cox PH			
		CSS2	95% CI	p	HR	95% CI	p	HR	95% CI	p (class)	p (variable)
Hyperlipidemia/statins category	H + S	0.548	42.7–65.3%	0.37	0.46
	nH	0.514	39.3–62.2%		1.13	0.7–1.81	0.62	0.86	0.48–1.53	0.61	.
	HnS	0.625	50.3–72.5%		0.79	0.48–1.31	0.36	1.28	0.69–2.37	0.44	.
5-year age categories	66–69	0.6	45.1–72%	0.05	< 0.01
	70–74	0.692	54.8–79.9%		0.67	0.34–1.28	0.22	0.58	0.28–1.22	0.15	.
	75 and older	0.487	39.3–57.4%		1.29	0.77–2.14	0.33	1.66	0.94–2.94	0.08	.
Sex	Male	0.575	49.3–64.9%	0.67	0.96
	Female	0.531	40.2–64.4%		1.1	0.71–1.69	0.67	1.01	0.62–1.66	0.96	.
Race/ethnicity	White NH	0.521	44.3–59.3%	0.02	0.12
	Non-white or Hispanic	0.708	55.8–81.6%		0.52	0.29–0.91	0.02	0.57	0.28–1.15	0.12	.
Marital status	Married or Partnered	0.692	59.4–77.1%	< 0.01	0.1
	Non-married	0.442	35–53.1%		2.15	1.41–3.3	< 0.01	1.5	0.93–2.43	0.1	.
Geographic region	West	0.663	56.4–74.5%	0.01	0.56
	East	0.447	28.7–59.5%		1.89	1.1–3.25	0.02	0.88	0.45–1.73	0.71	.
	Midwest	0.391	19.9–58%		2.66	1.43–4.95	< . 0.01	1.58	0.69–3.58	0.28	.
	South	0.519	37.7–64.4%		1.68	1–2.8	0.005	0.96	0.5–1.82	0.89	.
Patient location	Metropolitan	0.582	50.7–65%	0.08	0.38
	Non-Metropolitan	0.457	28.9–61%		1.55	0.93–2.56	0.09	0.73	0.36–1.49	0.38	.
Year of diagnosis	2008	0.538	39.5–66.2%	0.7	0.7
	2009	0.59	45.7–70.1%		0.9	0.51–1.58	0.71	0.93	0.49–1.74	0.81	.
	2010	0.509	37.1–63.1%		1.12	0.65–1.94	0.69	1.22	0.67–2.21	0.52	.
Tumor size stage	T0-1	0.679	47.3–81.8%	0.02	< 0.01
	T2	0.667	55–75.9%		1.04	0.49–2.21	0.93	1.17	0.49–2.82	0.73	.
	T3-4	0.446	34.3–54.4%		2.02	0.99–4.1	0.05	2.95	1.28–6.8	0.01	.
	Unknown	0.526	28.7–71.9%		1.69	0.67–4.27	0.26	1.78	0.63–5.01	0.28	.
Nodal stage	N0	0.585	47.1–68.3%	0.12	0.1
	N1	0.655	51.8–76.2%		0.81	0.46–1.4	0.45	0.88	0.45–1.74	0.71	.
	N2-3	0.468	35.3–57.4%		1.36	0.86–2.14	0.19	1.64	0.87–3.09	0.13	.
Comorbidity index	< 0.01	0.68	59.1–75.4%	< 0.0001	< 0.01
	1 or more	0.402	30.2–50%		2.37	1.58–3.57	< 0.0001	2.29	1.4–3.74	< 0.01	.
Most-visited facility was Teaching Hospital	No or unknown	0.569	47.1–65.6%	0.85	0.88
	Yes	0.556	45.7–64.3%		1.04	0.7–1.55	0.85	0.96	0.58–1.59	0.88	.
Tract pct high school only - Above Median	Not above Median	0.645	55.4–72.2%	< 0.01	0.04
	Above median	0.452	34.9–54.9%		1.82	1.21–2.72	< 0.01	1.88	1.03–3.43	0.04	.
Tract pct below poverty - Above Median	Not above Median	0.571	47.5–65.7%	0.71	0.96
	Above median	0.552	45.2–64.1%		1.08	0.72–1.61	0.71	0.99	0.58–1.67	0.96	.
Surgery	No	0.508	41.9–58.9%	0.03	< 0.01
	Yes	0.647	53.6–73.8%		0.63	0.41–0.97	0.03	0.31	0.17–0.57	< 0.01	.
Chemotherapy	No	0.513	39.8–61.5%	0.14	0.03
	Yes	0.591	50.4–66.8%		0.74	0.49–1.11	0.14	0.54	0.31–0.95	0.03	.
Radiation therapy	No radiation	0.3	12.3–50.1%	< 0.01	< 0.01
	Radiation	0.589	51.7–65.4%		0.39	0.22–0.7	< 0.01	0.24	0.11–0.54	< 0.01	.
Metformin	No	0.559	48.8–62.5%	0.83	0.09
	Yes	0.6	31.8–79.7%		0.92	0.4–2.1	0.83	2.46	0.86–7.08	0.09	.
Hypertension	No	0.607	46.7–72.1%	0.47	0.61
	Yes	0.547	46.7–62%		1.19	0.74–1.91	0.47	1.19	0.61–2.34	0.61	.
Diabetes	No	0.548	46.7–62.2%	0.57	0.13
	Yes	0.6	46.5–71.1%		0.88	0.55–1.39	0.57	0.63	0.34–1.14	0.13	.

*Other includes hypopharynx, nasopharynx, pyriform sinus, salivary glands.

Legend: OS2, percent 2-year overall survival; 95% CI, 95% confidence intervals; PH, proportional hazard; HR, hazard ratio.

the well-known adverse effects of statins such as myopathy and transaminitis were not included in this study, hospital and emergency room visits did not differ significantly between the three groups. The general tolerability of statins supports its use in cancer patients, especially in light of treatment modalities such as chemotherapy and radiation that pose significantly higher risks for toxicity.

Repurposing of medications not traditionally used for cancer treatment, such as statins, has become popular as costs for oncologic care have risen [23]. The results of this study, in combination with their

straightforward dosing, low cost, and extensive availability, make statins a potentially attractive treatment option for HNC patients in the future.

Our study carries significant limitations. Data of prognostic factors such as HPV status, tobacco use, alcohol consumption, and pathologic features were not included in the SEER-Medicare datasets; therefore, it is possible that these could have confounded our results. In addition, information about quality of life, locoregional control, and distant metastasis was also absent; studies using these outcome measures could

Table 5B
Cancer specific survival (other).

		Univariate Kaplan-Meier			Univariate Cox PH			Multivariate Cox PH			
		CSS2	95% CI	p	HR	95% CI	p	HR	95% CI	p (class)	p (variable)
Hyperlipidemia/statins category	H + S	0.643	49.3–76%	0.68	0.91
	nH	0.621	46.4–74.5%		1	0.52–1.92	1.00	1.06	0.46–2.46	0.9	.
	HnS	0.688	53.8–79.8%		0.77	0.39–1.51	0.45	0.88	0.35–2.19	0.78	.
5-year age categories	66–69	0.707	53.2–82.6%	0.39	0.08
	70–74	0.721	54.1–84%		0.89	0.38–2.09	0.78	0.57	0.21–1.54	0.27	.
	75 and older	0.593	47–69.7%		1.37	0.69–2.73	0.37	1.54	0.72–3.32	0.27	.
Sex	Male	0.682	57.9–76.5%	0.31	0.51
	Female	0.597	44.5–72.1%		1.33	0.76–2.32	0.31	1.25	0.65–2.4	0.51	.
Race/ethnicity	White NH	0.617	52–69.9%	0.05	0.35
	Non-white or Hispanic	0.77	57.1–88.6%		0.46	0.21–1.03	0.06	0.62	0.22–1.71	0.35	.
Marital status	Married or Partnered	0.729	60.8–81.9%	0.08	0.87
	Non-married	0.585	46.3–68.7%		1.65	0.94–2.9	0.08	1.06	0.54–2.07	0.87	.
Geographic region	West	0.735	61.8–82.1%	0.11	0.62
	East	0.556	33.7–72.8%		1.86	0.89–3.89	0.10	1.11	0.43–2.85	0.83	.
	Midwest	0.745	45.4–89.6%		1.28	0.44–3.74	0.65	0.74	0.18–2.99	0.67	.
	South	0.526	34.7–67.7%		2.07	1.08–3.96	0.03	1.57	0.66–3.71	0.31	.
Patient location	Metropolitan	0.656	56.3–73.3%	0.63	0.79
	Non-Metropolitan	0.649	43.1–80.1%		1.19	0.58–2.45	0.63	0.86	0.28–2.66	0.79	.
Year of diagnosis	2008	0.646	49.3–76.3%	0.91	0.96
	2009	0.641	50.4–75%		1.06	0.56–2.02	0.85	1.1	0.52–2.36	0.8	.
	2010	0.685	50.5–81%		0.92	0.45–1.86	0.81	1	0.46–2.17	0.99	.
Tumor size stage	T0-1	0.789	56.1–90.7%	0.07	0.05
	T2	0.721	57.2–82.6%		1.24	0.45–3.43	0.69	1.1	0.33–3.69	0.87	.
	T3-4	0.561	42.4–67.7%		2.37	0.91–6.15	0.08	2.91	0.92–9.19	0.07	.
	Unknown	0.556	26.4–77.2%		2.62	0.8–8.6	0.11	1.84	0.44–7.75	0.41	.
Nodal stage	N0	0.702	56.3–80.5%	0.18	0.16
	N1	0.742	56.9–85.3%		0.83	0.38–1.82	0.65	0.77	0.29–2.07	0.61	.
	N2-3	0.543	39.8–66.7%		1.53	0.82–2.83	0.18	1.74	0.74–4.1	0.2	.
Comorbidity index	< 0.01	0.725	61.7–80.8%	0.02	0.03
	1 or more	0.549	41.4–66.6%		1.9	1.1–3.28	0.02	2.2	1.09–4.44	0.03	.
Most-visited facility was Teaching Hospital	No or unknown	0.669	55–76.4%	0.82	0.96
	Yes	0.637	51.3–73.7%		1.06	0.62–1.83	0.82	1.02	0.5–2.09	0.96	.
Tract pct high school only - Above Median	Not above Median	0.703	58.9–79%	0.08	0.22
	Above median	0.581	44.9–69.2%		1.62	0.94–2.79	0.08	1.65	0.74–3.66	0.22	.
Tract pct below poverty - Above Median	Not above Median	0.65	52.7–74.8%	1.00	0.77
	Above median	0.658	53.6–75.4%		1	0.58–1.73	1.00	0.9	0.42–1.9	0.77	.
Surgery	No	0.588	48.1–68.1%	0.02	< 0.01
	Yes	0.766	62.1–86.2%		0.47	0.25–0.9	0.02	0.25	0.11–0.58	< 0.01	.
Chemotherapy	No	0.648	50.3–76%	0.39	0.08
	Yes	0.661	55.5–74.7%		0.79	0.45–1.38	0.40	0.48	0.21–1.09	0.08	.
Radiation therapy	No radiation	0.522	18.6–77.8%	0.27	0.22
	Radiation	0.662	57.5–73.6%		0.6	0.24–1.52	0.28	0.44	0.12–1.63	0.22	.
Metformin	No	0.635	54.7–71%	0.11	0.47
	Yes	0.909	50.8–98.7%		0.23	0.03–1.69	0.15	0.45	0.05–3.96	0.47	.
Hypertension	No	0.629	45.1–76.4%	0.86	0.71
	Yes	0.661	56.2–74.2%		0.95	0.51–1.75	0.86	0.83	0.32–2.17	0.71	.
Diabetes	No	0.608	50.6–69.6%	0.19	0.34
	Yes	0.765	61.5–86.3%		0.65	0.33–1.26	0.20	0.66	0.29–1.53	0.34	.

*Other includes hypopharynx, nasopharynx, pyriform sinus, and salivary glands.

provide further support for the use of statins in HNC patients. Furthermore, prescription data gathered from SEER-Medicare does not ensure that patients are actually taking their medications. Another limitation is the lack of statin-related toxicity data in the SEER-Medicare database, including myopathy and transaminitis. Lastly, SEER-Medicare patient demographics, including advanced age, may limit the generalizability of this study.

In summary, using SEER-Medicare patient databases, we demonstrate an association between statin use in HNC patients with hyperlipidemia with primary disease in the oral cavity and oropharynx and improved overall survival and cancer specific survival at 2 years

compared to both HNC patients with hyperlipidemia not using statins and HNC patients without hyperlipidemia. Statin use did not significantly increase cancer-related toxicity related events. In combination with the growing body of literature of statins’ ability to prevent carcinogenesis and tumor progression, these findings warrant additional prospective studies to further investigate the role of statins in HNC patients.

Conflict of interest

None declared.

Table 6
Toxicity.

	Total		nH		HnS		H + S		p (H + S vs. nH)	p (H + S vs. HnS)	
	N	%	N	%	N	%	N	%			
All patients	1592	100.0	495	100.0	567	100.0	530	100.0	.	.	
Weight loss	No	1040	65.3	314	63.4	366	64.6	360	67.9	0.13	0.24
	Yes	552	34.7	181	36.6	201	35.5	170	32.1	.	.
Antiemetics	No	842	52.9	275	55.6	275	48.5	292	55.1	0.88	0.03
	Yes	750	47.1	220	44.4	292	51.5	238	44.9	.	.
Emergency dept visit	No	1119	70.3	356	71.9	387	68.3	376	70.9	0.73	0.33
	Yes	473	29.7	139	28.1	180	31.8	154	29.1	.	.
Hospital/ED visit w/nausea/emesis/diarrhea	No	1313	82.5	407	82.2	462	81.5	444	83.8	0.51	0.32
	Yes	279	17.5	88	17.8	105	18.5	86	16.2	.	.
Hospital/ED visit w/dehydration	No	1159	72.8	363	73.3	401	70.7	395	74.5	0.66	0.16
	Yes	433	27.2	132	26.7	166	29.3	135	25.5	.	.
Hospital/ED visit w/malnutrition	No	1182	74.3	359	72.5	420	74.1	403	76.0	0.20	0.45
	Yes	410	25.8	136	27.5	147	25.9	127	24.0	.	.
Gastrostomy or Feeding Tube	No	979	61.5	301	60.8	335	59.1	343	64.7	0.20	0.06
	Yes	613	38.5	194	39.2	232	40.9	187	35.3	.	.
Dysphagia	No	834	52.4	261	52.7	290	51.2	283	53.4	0.83	0.46
	Yes	758	47.6	234	47.3	277	48.9	247	46.6	.	.
Esophageal stricture	No	1559	97.9	482	97.4	557	98.2	520	98.1	0.42	0.88
	Yes	33	2.1	13	2.6	10	1.8	10	1.9	.	.
Acute renal failure	No	1414	88.8	447	90.3	501	88.4	466	87.9	0.22	0.82
	Yes	178	11.2	48	9.7	66	11.6	64	12.1	.	.
Aspiration pneumonia	No	1455	91.4	453	91.5	506	89.2	496	93.6	0.21	0.01
	Yes	137	8.6	42	8.5	61	10.8	34	6.4	.	.
Tracheostomy or airway obstruction	No	1183	74.3	379	76.6	410	72.3	394	74.3	0.41	0.45
	Yes	409	25.7	116	23.4	157	27.7	136	25.7	.	.
Pneumonia	No	1293	81.2	404	81.6	450	79.4	439	82.8	0.61	0.14
	Yes	299	18.8	91	18.4	117	20.6	91	17.2	.	.
Speech pathology	No	1301	81.7	396	80.0	473	83.4	432	81.5	0.54	0.40
	Yes	291	18.3	99	20.0	94	16.6	98	18.5	.	.
Hospital/ED visit with neutropenia/thrombocytopenia	No	1461	91.8	455	91.9	517	91.2	489	92.3	0.84	0.52
	Yes	131	8.2	40	8.1	50	8.8	41	7.7	.	.

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