Title: **Statin Use and Head and Neck Squamous Cell Carcinoma Outcomes**

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Novelty and Impact: Statin medication use was associated with a lower rate of overall mortality in all patients, but was associated with a lower rate of disease-specific mortality and disease recurrence only among patients with HPV positive tumors. Our findings demonstrate that statin use may be protective for adverse outcomes in HNSCC patients, particularly those with HPV-positive disease. If true, these findings could have a meaningful impact on tertiary prevention for this cancer, which lacks evidence based recommendations.

Abbreviations: (ACE-27) Adult Comorbidity Evaluation 27 score, (BMI) Body Mass Index, (EMERSE) Electronic Medical Record Search Engine, (GED) General Education Development, (HNSCC) Head and Neck Squamous Cell Carcinoma, (HPV) Human Papillomavirus, (HR) Hazard Ratio, (IPW) Inverse Probability Weighting, (MV)-adj Multivariable Adjusted, (NDI) Social Security Death Index, (PCR) Polymerase Chain Reaction, (REDCap) Research Electronic Data Capture, (SPORE) Specialized Program of Research Excellence

Abstract

Head and neck squamous cell carcinoma (HNSCC) is a morbid cancer with poor outcomes. Statins possess anti-cancer properties such as immunomodulatory and anti-inflammatory effects. The objective of this study is to identify the association between statin use among untreated HNSCC patients and overall death, disease-specific death and recurrence. HNSCC patients were recruited to participate in the University of Michigan Head and Neck Cancer Specialized Program of Research Excellence (SPORE) from 2003-2014. Statin use data were collected through medical record review. Participants were considered a statin user if they used a statin at or after diagnosis. Outcome data were collected through medical record review, Social Security Death Index or LexisNexis. Our analytic cohort included 1,638 participants. Cox proportional hazard models were used to estimate the association between ever statin use and HNSCC outcomes. Statin use was seen in 36.0% of participants. We observed a statistically significant inverse association between ever using a statin and overall death (HR=0.75, 95%CI=0.63-0.88) and HNSCC-specific death (HR=0.79, 95%CI=0.63-0.99) and a non-statistically significant inverse association for recurrence (HR=0.85, 95%CI=0.70-1.04). When investigating the association between statin use and HNSCC outcomes utilizing interaction terms between statin use and human papillomavirus (HPV), statistically significant interactions for HNSCC-specific death and recurrence were identified (HNSCC-specific death: HPV-positive HR=0.41, 95%CI=0.21-0.84; HPV-negative HR=1.04, 95%CI=0.71-1.51; p-int-0.02; recurrence: HPV-positive HR=0.49, 95%CI=0.29-0.84; HPV-negative HR=1.03, 95%CI=0.74-1.43; p-int-0.02). Statin use may be protective for adverse outcomes in HNSCC patients, particularly those with HPV-positive disease. If true, these findings could have a meaningful impact on tertiary prevention for this cancer.

Background

Head and neck squamous cell carcinoma (HNSCC) is a debilitating disease with high morbidity and 5-year relative survival rate ranging from 31.9%-89.5% depending on the site of disease.[1] HNSCC arises from the mucosal lining of the aerodigestive tract starting in the nasal cavity and ending in the throat at the larynx, with other sites including the oral cavity, oropharynx, and hypopharynx.[1–3] The epidemiology of HNSCC has changed over the past decades in the United States due to a shift in the major risk factors associated with certain disease sites. There has been a decrease in the number of patients with HNSCC of the oral cavity and larynx in the United States which may be explained by the large decrease in smoking over time, the main risk factor for HNSCC in these sites.[4,5] Human papillomavirus (HPV) positive HNSCC, which is predominantly found in the oropharynx, has been increasing in the United States over the past decades.[6] HPV-positive disease has better prognosis than HPV-negative HNSCC and appears to be more responsive to treatment.[7] This may be related to the difference in patient characteristics between patients with HPV-positive tumors and patients with HPV-negative HNSCC.[6,7]

Although treatment options have improved and expanded over the decades there are still no evidence-based tertiary prevention strategies for HNSCC other than tobacco cessation. Statins are a class of commonly prescribed medications that are primarily used to lower cholesterol.[8] In addition, statins exhibit anti-cancer effects including anti-inflammatory and immunomodulatory properties.[9] Thus, it is hypothesized that they may prevent the development or progression of cancer through these mechanisms or through cholesterol lowering.[9] Cholesterol may be an essential factor in cancer development or progression because it is involved in various pathways associated with carcinogenesis.[10]

Numerous studies have investigated the association between statin use and cancer outcomes among different cancer sites and have found protective results, but the literature is limited when

investigating this association among HNSCC patients.[11,12] The few studies that have investigated this association found a protective association between statin use and the development of HNSCC as well as a protective association between the use of statins and overall death and HNSCC-specific death.[13–15] Although these analyses provide promising results they had some important limitations. First, they did not adjust for some important confounding variables in their models, notably characteristics such as BMI. Further, none of these studies examined HPV-positive and HPV-negative disease separately other than through the elimination of certain disease sites from analysis.[14] This is important because HPV-positive HSNCC is increasing in the US and have different pathogeneses and immune/inflammatory response modulation.[1] They also did not investigate the association between statin use and disease recurrence as an outcome.

The objective of this study is to examine the association between statin use and HNSCC survival outcomes in a large prospective cohort of previously untreated HNSCC patients, with thorough adjustment for potential confounding factors and examining HPV-positive and negative disease separately.

Material and Methods

Study Population

This study includes incident cases of HNSCC who participated in the University of Michigan Head and Neck Cancer Specialized Program of Research Excellence I and II (SPORE I and SPORE II). Participants in SPORE I were diagnosed and recruited from 2003-2008 and recruitment for SPORE II participants started in 2008 and ended in 2014. Subjects were eligible for participation if they were over the age of 18 years old, newly diagnosed with disease, and had not previously received treatment for their cancer. A more in-depth explanation of the study recruitment and procedures has been published previously.[16,17] There were 1,648 patients who

were recruited through the University of Michigan in SPORE I (N=606) and SPORE II (N=1,042). Of the patients who participated in the Head and Neck Cancer SPORE, 1,638 participants had complete information on statin use.

Exposure

Information on use of selected medications, including statins, at any point during follow-up was previously collected for SPORE I participants from the medical record. For the current analysis, medication information for SPORE II participants was newly collected through medical record abstraction. The following statins were used among SPORE II participants: Atorvastatin (Lipitor, Caduet)= 23.7%, Lovastatin (Mevacor)=9.9%, Pravastatin (Pravachol)=11.7%, Rosuvastatin (Crestor)=9%, Simvastatin (Simcor, Zocor, Vytorin)=46.5%; total does not equal 100% because categories were not mutually exclusive, 3 participants reported taking 2 different statins. Comprehensive information on medication use was routinely collected by physicians prior to initiating treatment. Patients were asked if they were currently using any medications. If yes, the name of the medication was recorded in the medical record. The initial visit related to the patient's HNSCC diagnosis at the University of Michigan Rogel Cancer Center was identified in the electronic medical record and all medications reported were abstracted from that encounter, if available. If this information was not available during that encounter the information was abstracted from closest encounter to the initial encounter date but prior to treatment initiation. To identify if participants started a statin after diagnosis, electronic medical record search engine (EMERSE) was used to search for statin medication names throughout the medical record.[18] If a participant was identified as using a statin at or after diagnosis they were classified as ever using a statin. In addition to investigating the exposure as ever statin use, we also investigated the association between statin use at diagnosis and HNSCC outcomes, among the SPORE II participants for whom pre- and post-diagnosis use could be differentiated. Trained research personnel collected the exposure information from all participants if available. The

inter-rater reliability was quite high between abstractors with a Kappa value of approximately 95%. Patient records that were not concordant were reviewed by both abstractors and reconciled. All data were stored in a Research Electronic Data Capture (REDCap) database.[19]

Outcome

Patients seen at the University of Michigan were annually monitored for overall death, disease-specific death and recurrence through medical record review and patient follow-up. Recurrence of disease was defined as patients who were identified as never being free of disease, as well as those who experienced distant, local or regional recurrence of disease. Beyond this surveillance, linkage with the national social security death index (NDI) to ascertain participant survival was conducted annually. After study follow-up was complete a final update of the participants' survival status was conducted through LexisNexis. If a participant was in the NDI, or if a family member informed us that they had died, medical records or resources through LexisNexis were reviewed by trained study personnel to determine the date of death and whether the death was due to HNSCC or another cause. Death or recurrence information was reviewed by physicians for accuracy. Participants' outcome information was collected and updated through April 2016.

Confounding Variables

Information on potential confounding variables were collected through various data sources. Confounders related to behaviors such as smoking and drinking were collected through health surveys that were completed yearly by patients. Demographic and clinically related confounders such as race, gender, age, body mass index (BMI) and Adult Comorbidity Evaluation 27 score (ACE-27) were collected through the patient's medical record. There were several effect modifiers that we assessed; HPV status, disease site and stage at diagnosis. HPV status was identified through the following testing; polymerase chain reaction (PCR) testing, and in situ

hybridization, both of which have high sensitivity and specificity (>80%).[20] If tissue was not tested for HPV status from a previously conducted sub-study of SPORE I or SPORE II it was obtained through the patient's medical record or pathology reports.

All models were adjusted for age at diagnosis as a continuous variable. The following factors that are hypothesized or known to be associated with either HNSCC outcomes or statin use were considered as potential confounding variables: gender, race, ACE-27, smoking, BMI, education and stage. Certain clinical variables thought to be associated with HNSCC survival that are often adjusted for in survival analyses, such as site of disease and HPV status, were not independently associated with the use of statins in our data. Each potential confounder was entered into the age-adjusted model to evaluate whether the point estimates for statin use changed by at least 10%. The variables that impacted the association between statin use and HNSCC outcomes the most were age, ACE-27, and BMI. Other potential confounders were added to the model individually and cumulatively, but their inclusion resulted in a less than 10% magnitude change in the point estimates. The most parsimonious and final model includes only age, ACE-27 and BMI as confounders. We also presented results from a fully adjusted model (adjusted for, age (continuous), BMI (<25, 25-<30, 30+ kg/m^2, missing), ACE-27 (none, mild, moderate, severe), gender (female, male), education (less than high school, high school or General Education Development (GED), some college, 4 year degree, more than 4 year degree, missing), race (white, not white, missing), smoking status (never, former, current, missing), drinking status (never, former, current, missing), and stage of disease (0 or 1, 2, 3, 4). Only 7 participants were missing information for ACE-27 so these individuals were included in the most common category (Mild) for adjustment, as there were too few for a separate missing category.

Statistical Analysis

Descriptive and bivariate analysis was conducted to compare demographic, behavioral and clinical characteristics between participants who were considered ever statin users compared to

those who did not use a statin at or after diagnosis. Statistical significance was determined through chi-square tests for categorical variables and t-tests for continuous variables.

Cox proportional hazard models were used to estimate the association between ever statin use and overall and disease-specific death as well as disease recurrence. For recurrence, we began follow-up at the time of diagnosis. Patients who experienced recurrence ended follow-up at the date of documented recurrence. Participants who did not experience recurrence were censored at last follow-up. Similarly, for progression to disease-specific or overall death, follow-up began at the time of diagnosis. For disease-specific death, participants who did not die due to malignancy were censored at the time of death due to other causes or last follow-up. Follow-up ended for participants who did die from malignancy at the time of death. For overall death, participants who did not die were censored at the end of follow-up. Follow-up ended for participants who died at the time of death. We estimated the hazard ratio (HR) of recurrence, overall death, and disease-specific death for ever statin use (versus non-use). We also estimated the HR of recurrence, overall death, and disease-specific death for statin use at diagnosis (versus non-use) among SPORE II participants, as explained above. The proportional hazards assumption was confirmed through conducting interaction models with time.

In this study we investigated if effect modification was present across HPV status, disease site and stage of disease. Subgroup analyses were conducted stratifying by disease site (HPV-positive associated disease sites: oropharynx vs. HPV-negative associated disease sites: oral cavity, larynx, hypopharynx and other), stage of disease (stage 4 vs. stages 0-3), and HPV status (HPV-positive, HPV-negative, HPV status invalid/missing). Statistical interaction was evaluated using the likelihood ratio test. HPV status was missing for approximately half of the participants (49.45%). Thus, in order to identify if missing HPV status biased the point estimates we conducted various sensitivity analyses. We kept the participants with missing HPV status as a separate category, dropped the participants with HPV status missing and used stabilized

inverse probability weighting (IPW) to weigh participants to emulate the population if no one was missing HPV status. In order to calculate stabilized inverse probability weights logistic regression models were conducted to calculate the probability of not having HPV status missing. The predictors in this model included: year enrolled in the study, age, gender, smoking status, drinking status, marital status, stage of disease, ACE-27 scores, disease site and BMI. Observations with values missing for the predictors in the model were dropped from the analysis and are missing probabilities. Probabilities generated from this model were the denominators of the weights. An intercept only model for the probability of not having HPV status missing was conducted. The probabilities calculated from the intercept only model were the numerator of the weights and were used instead of the value 1 to standardize the distribution of the weights, which allows provides a more normal distribution. Participants who have similar predictors to those who are missing HPV status will have higher weights in the final model and participants missing HPV status were dropped.

All analyses were conducted using SAS version 9.4 (Cary, NC). All tests were two-sided, and results were considered statistically significant if $p<0.05$.

Results

Descriptive statistics of statin use across baseline demographic and clinical characteristics are displayed in Table 1. In the study cohort, 36.0% of participants ever used a statin. Participants who used a statin were on average older, were more likely to be white, overweight or obese, or former smokers and drinkers, to have mild ACE-27 scores, and were more highly educated.

Over the follow-up period (657) 40.1% of participants in the study died due to any cause and (379) 23.1% died from HNSCC. Disease recurrence occurred in 30.2% (495) of participants. We observed a statistically significant inverse association between ever statin use and the rate of overall [multivariable adjusted (MV)-adj HR= 0.75; 95% CI= (0.63, 0.88)] and disease-specific

[MV-adj HR= 0.79; 95% CI= (0.63, 0.99)] death among HNSCC patients in this study (Table 2). Similarly, we observed a suggestive inverse association between ever statin use and disease recurrence [MV-adj HR= 0.85; 95% CI= (0.70, 1.04), Table 2]. Results from the fully adjusted model were similar (Table 2). Additional analyses were conducted to identify if the association between statin use and HNSCC outcomes was still present after excluding participants who had distant metastatic disease at diagnosis (N=44) as well as excluding participants who died within 6 months of diagnosis (N=104) (Supplemental Materials, Table 1); results from these additional analyses are consistent with the findings presented in Table 2.

When we examined participants with HPV-positive and HPV-negative tumors separately, excluding participants who were missing HPV status, we observed a protective association between statin use and overall death for those in the HPV-positive [MV-adj HR= 0.52; 95% CI= (0.31, 0.86)], and HPV-negative [MV-adj HR= 0.76; 95% CI= (0.57, 1.02)] groups. However, when we examined the association between statin use and rate of disease-specific death we observed a significant interaction such that this inverse association was only observed for patients who were HPV-positive [HNSCC-specific death: MV-adj HR= 0.41; 95% CI= (0.21, 0.84)] and null for patients who were HPV-negative, HNSCC-specific death: [MV-adj HR= 1.04; 95% CI= (0.71, 1.51)], p for interaction = 0.02 (Table 3). This protective relationship was also observed for HPV-positive patients' rate of recurrence: [MV-adj HR= 0.49; 95% CI= (0.29, 0.84)] while a null association for patients whose tumor HPV status was negative was observed: [MV-adj HR= 1.03; 95% CI= (0.74, 1.43)], p for interaction=0.02. Results were very similar when we excluded participants who had distant metastatic disease (Supplemental Materials, Table 2) as well as when we included a missing category for HPV status or when IPW was used to address missingness (Supplemental Materials, Table 3). Results remain inverse for HPV positive patients when conducting the analysis among participants in SPORE 2 for statin use at baseline.

When excluding participants who were missing HPV status, we observed a protective association for the relationship between statin use at diagnosis and overall death among participants who were HPV-positive and who were HPV-negative but neither these results nor the interaction term were statistically significant. The association between statin use at diagnosis and HNSCC-specific death as well as recurrence were similar to the association that was displayed above between ever statin use and HNSCC-specific death and recurrence. Results for the HNSCC-specific death associations were, HPV-positive: [MV-adj HR= 0.53; 95% CI= (0.21, 1.31)], HPV-negative: [MV-adj HR= 1.19; 95% CI= (0.76, 1.85)], (p for interaction= 0.09) and for recurrence HPV-positive: [MV-adj HR= 0.51; 95% CI= (0.25, 1.03)], HPV-negative: [MV-adj HR= 1.14; 95% CI= (0.77, 1.69)], (p for interaction=0.04).

We found a statistically significant inverse association between ever statin use and recurrence for the stratified analysis among participants whose site of disease was located in the oropharynx compared to those who never took a statin (Table 3), but these results were not as strong as those observed in the HPV stratified analysis. We observed no statistically significant interaction by stage (Table 3).

Discussion

In this large prospective study of HNSCC patients, we observed a protective association between statin use and disease-specific death and recurrence that was restricted to HPV-positive patients. However, statins were protective for overall death in all patients. To our knowledge this is the first paper to investigate the association between statin use and HNSCC outcomes stratified by HPV status and with comprehensive adjustment for potential confounding factors (Table 2).

Two previous studies observed a protective association for both HNSCC overall death and disease-specific death. One of these studies only included HNSCC disease sites that are not

associated with HPV-positive disease and the other study did not consider HPV status in their analyses.[14,15] To our knowledge, the present analyses are the first to consider the role of HPV status in the statin-HNSCC outcome association. Importantly, neither of these previous studies adjusted for BMI in their analyses.[14,15] Higher BMI has been found to be protective against adverse HNSCC outcomes.[21–23] Further, according to the American College of Cardiology and the American Heart Association, obesity is a risk factor for developing heart disease and statin use is recommended for people who are at "borderline or intermediate risk" for cardiovascular disease, making statin use more common among individuals with a higher BMI.[24] Thus, BMI would be a positive confounder of the statin-HNSCC outcome association, and failing to adjust for this confounder could have biased their results toward a more protective association than is actually present. In fact, in the present analysis, our results were markedly attenuated when we adjusted for BMI. This may explain the apparently discrepant findings between previous studies that found a protective association even among patients who were likely HPV-negative.

Our findings are consistent with the potential biological impact of statin drugs on cancer cells. Statins possess anti-inflammatory and immunomodulatory effects and these effects may influence cancer.[9,25] There have been studies to suggest the presence of certain inflammatory markers may improve HNSCC outcomes such as tumor infiltrating lymphocytes, or make HNSCC outcomes worse such as the pro-inflammatory cytokine, IL-6.[17,26,27] Although there do not appear to be any studies about the production of inflammatory markers and statin use among patients with HNSCC, there are a few studies that have investigated the use of statins and the presence of inflammatory biomarkers among the general population and among patients with hypercholesterolemia. Some studies found a reduction in the number of circulating pro-inflammatory cytokines among statin users.[28–31] Statins have also been associated with the increased production of T-cells in mice and lung tumor cell lines, and as mentioned above the presence of T-cells in tumors are often associated with better outcomes among HNSCC

patients.[32] Thus, anti-inflammation and immune modulation are plausible mechanisms by which statins may provide protection against adverse outcomes in HNSCC patients specifically among patients whose disease is HPV-positive. This association may be related to the known pro-inflammatory and active immune response seen predominantly in HPV-positive HNSCC, however further research is needed to establish the biologic mechanism by which statins are protective.[26,27,33–37]

Strengths and limitations

The strengths of the study are a large sample size representing various sites of HNSCC, excellent survival ascertainment, and information on many clinical tumor characteristics, potential confounders, and effect modifiers. One possible limitation is that, although the data available at diagnosis for patients was collected systematically, the data collected post diagnosis was not consistently available for all participants depending upon whether they attended the University of Michigan for routine follow-up care. This may lead to misclassifying participants as never statin users who may have started a statin after diagnosis but were lost to follow-up. If statins are truly protective against cancer outcomes as the literature suggests this would bias our estimates toward the null, meaning the true association may be even stronger than what we observed. It is possible that participants who are very ill prior to study recruitment or HNSCC diagnosis may discontinue medication/statin use. We may potentially misclassify those participants as never statin users which may lead to observing a stronger protective association than what is expected. To mitigate this issue we conducted a sensitivity analysis that excluded participants who had distant metastatic disease and those who passed away within 6 months of diagnosis (Supplemental Table 1). After excluding participants with distant metastatic disease we still observed a statistically significant interaction such that we observed an inverse association between statin use and both disease-specific death and recurrence only among HPV-positive patients (Supplemental Table 2). Using an ever statin use variable may

lead to immortal time bias, which leads to possible misclassification of the exposure variable because participants may start statins after diagnosis or discontinue statin use at any point in the study. This would lead to misclassifying participants as statin users during periods of time in which they were not using a statin. However, when we considered use of statins at baseline only among the SPORE II participants, our results for the HPV-positive patients remained inverse, although they were no longer statistically significant, likely due to the reduction in sample size. It should be noted that among SPORE II participants, 32.2% were statin users at diagnosis and only a small minority of participants initiated statin use after diagnosis (7.1%), making this source of bias likely to be minimal. Additional studies with detailed information on statin use are needed to fully address this possible source of bias.

Lastly, we were unable to investigate the dose response relationship between statin use and HNSCC outcomes; this information was not available for all participants through their medical record. Future research is necessary to investigate if there is a dose response relationship between statin use and HNSCC outcomes as well as duration of statin use and HNSCC outcomes.

Conclusion

Our findings from this large, prospective study demonstrate that statin use may be protective for adverse outcomes in HNSCC patients, particularly those with HPV-positive disease. If true, these findings could have a meaningful impact on tertiary prevention for this cancer, which lacks evidence based recommendations.

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Data Availability Statement: The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: None

Ethics Statement: Patients recruited through SPORE I and SPORE II provided written informed consent, and the medical record review and SPORE studies were approved through the University of Michigan Medical School's Institutional Review Board.

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For certain cancer types, statin medications reduce the risk of disease development and death, possibly owing to the immune-modifying or cholesterol-lowering effects of statins. Whether head and neck squamous cell carcinoma (HNSCC) is among these cancers affected by statins remains unclear. In this study of more than 1,600 HNSCC patients, statin use was associated with a reduced overall mortality rate in all patients and with a reduced rate of disease-specific mortality and disease recurrence specifically among patients with human papillomavirus-positive tumors. Inverse associations were also observed between statin use and recurrence among participants with disease located in the oropharynx.

Tables

Table 1. Demographic and Clinical Characteristics by Statin use

	Ever Statin User (N=589, 35.96%)	Never Statin User (N=1049, 64.04%)	P-value
Age at Diagnosis, years	63.49	57.79	<.0001
Sex (Male)	73.17%	74.55%	0.54
Race			0.006
White	93.89%	91.80%	
Not white	3.40%	6.67%	
Missing	2.72%	1.53%	
Disease Site			0.78
Larynx	17.83%	18.40%	
Oral Cavity	33.28%	31.74%	
Oropharynx	36.16%	38.42%	
Hypopharynx	3.74%	3.81%	
Other	9.00%	7.63%	
Stage at Diagnosis			0.47
0	2.04%	1.53%	
1	12.05%	10.87%	
2	11.54%	9.91%	
3	14.26%	13.16%	
4	60.10%	64.54%	
Treatment			0.27
Surgery alone	21.39%	18.78%	
Surgery + adjuvant radiation	11.21%	10.10%	
Surgery + adjuvant chemoradiation	8.66%	10.20%	
Radiation alone	6.96%	6.01%	
Chemoradiation alone	40.07%	39.18%	
Chemotherapy alone	2.55%	3.34%	
Palliative, unknown	9.17%	12.39%	
HPV status			0.47
Negative	29.54%	26.79%	
Positive	22.58%	22.88%	
Invalid/Missing	47.88%	50.33%	
ACE Score[a]			<.0001
None	13.41%	33.75%	
Mild	46.86%	41.94%	
Moderate	26.99%	16.97%	
Severe	11.88%	7.15%	
Missing	0.85%	0.19%	
Highest Education			0.008
Less than high school	4.75%	9.44%	

High school/GED	24.28%	24.79%	
Some College	28.52%	25.83%	
4 yr degree	8.32%	8.96%	
More than 4 year degree	12.05%	8.87%	
Missing	22.07%	22.12%	
BMI			<.0001
Underweight/Normal Weight	25.64%	43.76%	
Overweight/Obese 1	57.05%	46.04%	
Obese 2/Obese 3	13.75%	8.10%	
Missing	3.57%	2.10%	
Smoking Status			<.0001
Current	32.77%	47.95%	
Former	40.24%	25.55%	
Never	23.94%	24.79%	
Missing	3.06%	1.72%	
Drinking Status			<.0001
Current	55.86%	68.06%	
Former	29.71%	21.16%	
Never	11.04%	9.06%	
Missing	3.40%	1.72%	

Table 2. Multivariable Cox Proportional Hazards Models of Ever use of Statins and HNSCC Outcomes

	No. of Events	Person-Months	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]	HR (95% CI)[d]
Overall Death	657					
Statin Use						
No	432	55627.60	1	1	1	1
Yes	225	29847.95	0.95 (0.81, 1.11)	0.78 (0.66, 0.92)	0.75 (0.63, 0.88)	0.74 (0.62, 0.88)
HNSCC Death	379					
Statin Use						
No	250	55627.60	1	1	1	1
Yes	129	29847.95	0.91 (0.74, 1.13)	0.80 (0.64, 0.99)	0.79 (0.63, 0.99)	0.78 (0.61, 0.98)
Recurrence	495					
Statin Use						
No	318	34653.14	1	1	1	1
Yes	177	19442.40	0.97 (0.81, 1.17)	0.86 (0.71, 1.04)	0.85 (0.70, 1.04)	0.84 (0.69, 1.02)

a. Unadjusted analysis
b. Age-adjusted analysis
c. Adjusted for age, BMI and ACE-27
d. Adjusted for age, BMI, ACE-27, gender, education, race, smoking status, drinking status and stage of disease (0 or 1, 2, 3, 4)

Table 3. HPV, Stage and Disease Site Stratified Analysis

	Never Statin User			Ever Statin user		
Effect Modifiers	**No. of Events**	**Person Months**	**HR (95% CI)[a]**	**No. of Events**	**Person Months**	**HR (95% CI)[a]**
HPV status						
Overall Death						
HPV-Positive	61	12943.93	1 (REF)	21	7660.39	0.52 (0.31, 0.86)
HPV-Negative	131	12916.80	1 (REF)	80	7560.38	0.76 (0.57, 1.02)
P for interaction				0.18		
Disease-Specific Death						
HPV-Positive	38	12943.93	1 (REF)	10	7660.39	0.41 (0.21, 0.84)
HPV-Negative	71	12916.80	1 (REF)	52	7560.38	1.04 (0.71, 1.51)
P for interaction				0.02		
Recurrence						
HPV-Positive	55	8814.55	1 (REF)	18	5798.21	0.49 (0.29, 0.84)
HPV-Negative	95	8996.63	1 (REF)	68	5028.99	1.03 (0.74, 1.43)
P for interaction				0.02		
Stage						
Overall Death						
Stage 4	313	34729.56	1 (REF)	155	17522	0.68 (0.56, 0.83)
Stage 0-3	119	20898.04	1 (REF)	70	12325.95	0.82 (0.61, 1.10)
P for interaction				0.32		
Disease-Specific Death						
Stage 4	195	34729.56	1 (REF)	97	17522	0.74 (0.58, 0.96)
Stage 0-3	55	20898.04	1 (REF)	32	12325.95	0.83 (0.54, 1.29)
P for interaction				0.67		
Recurrence						
Stage 4	237	21384.74	1 (REF)	120	11211.86	0.78 (0.62, 0.99)
Stage 0-3	81	13268.40	1 (REF)	57	8230.54	0.99 (0.70, 1.39)
P for interaction				0.26		
Disease Site						
Overall Death						
Oropharynx	144	23395.71	1 (REF)	64	12503.82	0.64 (0.48, 0.87)
Other site	288	32231.89	1 (REF)	161	17344.13	0.80 (0.66, 0.98)
P for interaction				0.22		
Disease-Specific Death						
Oropharynx	87	23395.71	1 (REF)	35	12503.82	0.64 (0.43, 0.96)
Other site	163	32231.89	1 (REF)	94	17344.13	0.87 (0.67, 1.13)
P for interaction				0.21		
Recurrence						
Oropharynx	111	14423.62	1 (REF)	44	8470.44	0.62 (0.43, 0.88)
Other site	207	20229.52	1 (REF)	133	10971.96	0.99 (0.79, 1.24)
P for interaction				0.02		

a. Adjusted for Age at diagnosis, BMI and ACE-27