Am J Cancer Res 2021;11(5):2343-2350
www.ajcr.us /ISSN:2156-6976/ajcr0129006

Original Article

Association of pretreatment body mass index with risk of head and neck cancer: a large single-center study

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Received December 25, 2020; Accepted March 10, 2021; Epub May 15, 2021; Published May 30, 2021

Abstract: Smoking and alcohol exposure continue to be the dominant risk factors for the development of head and neck squamous cell carcinoma (SCCHN) worldwide. Moreover, human papillomavirus (HPV) is associated with SCCHN, particularly SCC of the oropharynx (SCCOP). Body mass index (BMI) has been reported as a possible risk factor for SCCHN, yet the data available so far about the relationship between BMI and SCCHN risk have been mixed. We sought to clarify this relationship. BMI and demographic, clinical, and epidemiological information at diagnosis were collected from 2310 SCCHN cases and 1915 controls (who were cancer-free) from October 2001 through May 2013. The odds ratios (ORs) and 95 percent confidence intervals (95% CI) were determined using the logistic regression process. Multivariable models were used to evaluate the strength of the relation between BMI and SCCHN risk. At diagnosis, 64 (2.8%) of the cases were underweight (BMI <18.5 kg/m^2), 661 (28.6%) were normal weight (BMI 18.5<25 kg/m^2), 833 (36.1%) were overweight (BMI 25<30 kg/m^2), and 752 (32.6%) were obese (BMI ≥30 kg/m^2). Comparatively, the ORs (95% CIs) for SCCHN associated with being underweight, overweight, and obese were 2.6 (1.54.7), 0.7 (0.6-0.8), and 0.8 (0.7-0.9), respectively, after adjusting for age, gender, race/ethnicity, smoking, and alcohol consumption. On analysis stratified by tumor sites, the risk of SCCOP among patients seropositive for HPVE6 and/or HPVE7 was higher among the overweight (OR, 5.4, 95% CI, 1.3-23.1) and obese patients (OR, 2.4, 95% CI, 1.1-7.6) compared to the normal weight patients. These findings suggest that pretreatment BMI could be a major risk factor for SCCHN, and the association between BMI and HPV may increase the risk of SCCOP.

Keywords: Body mass index, squamous cell carcinoma of the head and neck, oropharyngeal cancer, human papillomavirus, sexual behavior, case-control study

Introduction

At the time this study commenced there were approximately 630,000 new diagnoses of squamous cell carcinoma of the head and neck (SCCHN) and 350,000 deaths from this disease worldwide annually [1]. Consumption of tobacco and alcohol, as well as human papillomavirus (HPV) infection, are common risk factors for SCCHN, and thus prevention remains paramount to reduce the morbidity and mortality of SCCHN [1]. It is also critical to identify other potential modifiable risk factors associated with SCCHN.

Obesity or high body mass index (BMI) has been found to be closely related to the risk of a number of cancers [2-4]. In the United States (US), BMI in adults has risen exponentially in the last several years, with an estimated increase in weight between 1999-2000 and 2015-2016 of over 8 pounds in men and 7 pounds in women [5]. BMI has previously been related to a higher risk of SCCHN by the International Agency for Research on Cancer study [6]. However, as a result of previous studies' limited sample sizes, the results in regard to the relation between BMI and risk of SCCHN were inconclusive. Previous studies presented that high BMI was related with a lower risk of SCCHN, while others indicated that low BMI was associated with reduced risk [6]. Further, the potential association between HPV serological status and BMI has yet to be fully elucidated.

BMI may play different roles in the development of SCCHN at different tumor sites. So, it is cru-

cial to consider the primary tumor site in assessments of the correlation between BMI and SCCHN risk. Few studies have examined the role of BMI and HPV in the development of SCCHN, particularly squamous cell carcinoma of the oropharynx (SCCOP). HPV infection, a sexually transmitted infection, is widely recognized as an etiological agent of nearly all cervical cancers and of the majority of anogenital cancers and SCCOPs [7]. Additionally, HPV has been responsible for a rapid increase in the incidence of SCCOP between 1992 and 2000 in developed countries [7]. As projected, SCCOP now exceeds cervical cancer as the HPV-associated cancer with the highest incidence in the US [7]. Previous studies note that sexual behaviors before diagnosis are significantly associated with HPV-positive SCCOP but not with HPV-negative SCCOP [8].

To date, the association between BMI and SCCHN risk remains unclear because of the conflicting findings of previous studies and limited statistical power [6]. Therefore, we attempted to identify whether pretreatment BMI is related to SCCHN risk while controlling for various confounders including tobacco use, alcohol use, and HPV infection. Our secondary objective was to determine whether HPV status and sexual behavior play a role in the association of pretreatment BMI with SCCHN risk.

Methods

Study subjects

From October 2001 through May 2013, 4225 study subjects were recruited in a systematic manner through the Head and Neck Surgery Clinic at The University of Texas MD Anderson Cancer Center in Houston, Texas. The MD Anderson Cancer Center's institutional review board (IRB) gave its approval to the study. Informed consent was acquired from all participants in the study.

Eligible cases were consecutive patients with incident, histologically confirmed SCC with diagnosis codes 141, 143-146, 148, 149, and 161 concurring to the International Classification of Disease, Ninth Revision (carcinoma of the oral cavity, oropharynx, and hypooropharynx). Patients were excluded if they had second primary SCCHN tumors, nasopharyngeal or sinonasal tract primary tumors, tumors found outside the upper respiratory tract, cervical metastases of unknown origin, or other histopathologic conditions [9]. Around 95% of qualifying patients who were approached decided to participate in the study. Patients who agreed to participate were asked about lifetime sexual practices and history of sexually transmitted diseases before the cancer diagnosis.

The study included 1915 individuals (controls) who were recruited at the same time, given the fact that they were biologically unrelated to the patients seen at The University of Texas MD Anderson Cancer Center in Houston, Texas [10]. Age (± 5 years), sex, and race were used to match the controls to cases. Following the signing of IRB-approved informed consent form, participants in the study filled out a demographic and medical questionnaire. The control group had a response rate of more than 80% [11].

Data collection

BMI and demographic, clinical, and epidemiological data on study subjects were collected from questionnaires and medical records. BMI in controls was calculated using information in the survey questionnaire; BMI in cases was calculated from pretreatment metrics dividing the weight in kilograms by the square of height in meters [12]. Participants were categorized on the basis of BMI as underweight (BMI less than 18.5 kg/m^2), normal or healthy weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), or obese (BMI greater than 30.0 kg/m^2) in agreement with CDC guidelines [12]. The TNM staging system 8th edition of the American Joint Committee on Cancer (AJCC) was used to assess the stage at the time of presentation. Participants who had smoked more than hundred cigarettes in their lifetimes were classified as "ever-smokers" and those who had smoked less than hundred were grouped as "never-smokers". "Ever-drinkers" were those who drank alcoholic drinks at least once a week for more than a year, while "never-drinkers" were those who did not [11].

Determination of HPV status

After histopathologic confirmation of SCCHN, the occurence of HPV 16/18 DNA was examined in paraffin-embedded tumor specimens. In summary, DNA was obtained from tissue DNA extraction kit (Qiagen Inc., Valencia, CA) and screened for HPV 16/18 DNA using PCR

Table 1. Characteristics of cases and controls[a]

Characteristic	No. (%) Cases (*N* = 2310)	No. (%) Controls (*N* = 1915)	*P* value
Age, years			
<50	478 (20.7)	572 (29.9)	<0.0001
≥50	1832 (79.3)	1343 (70.1)	
Sex			
Male	1778 (77)	1403 (73.3)	0.005
Female	532 (23)	512 (26.7)	
Race/ethnicity			
Non-Hispanic white	1989 (86.1)	1638 (85.5)	0.598
Other	321 (13.9)	277 (14.5)	
Smoking status			
Ever smoker	1559 (67.5)	924 (48.3)	<0.0001
Never smoker	751 (32.5)	991 (51.8)	
Alcohol use status			
Ever user	1682 (72.8)	1055 (55.1)	<0.0001
Never user	628 (27.2)	860 (44.9)	
BMI[b]			
Underweight	64 (2.8)	16 (0.8)	<0.0001
Normal	661 (28.6)	425 (22.2)	
Overweight	833 (36.1)	791 (41.3)	
Obese	752 (32.6)	683 (35.7)	
Tumor site			
Oral cavity	708 (30.6)	-	
Oropharynx	1179 (51)	-	
Hypopharynx or larynx	421 (18.2)	-	
Stage			
I/II	551 (24)	-	
III/IV	1750 (76)	-	
Comorbidity			
None/mild	1978 (85.6)	-	
Moderate/severe	332 (14.4)	-	
Primary treatment			
Surgery only	376 (16.3)	-	
Chemoradiotherapy	1934 (83.7)	-	

[a]Values in table are number of patients (percentage) unless otherwise indicated. [b]Body mass index (BMI) is a person's weight in kilograms divided by the square of the height in meters.

assays with primers specific for the E6 and E7 regions, as well as positive and negative controls. These controls along with β-actin as a quality control were run in triplicate with the samples [13].

Statistical analysis

The Chi-square and Fisher's exact tests were used to assess the variations in characteristics between cases and controls. The crude odds ratios (ORs) and 95 percent confidence intervals (95% CI) were determined using the unconditional logistic regression process. The multivariate models were also performed with adjustment for several potential confounders. Further stratified analysis was performed for the association of BMI with SCCHN risk by age, sex, race/ethnicity, smoking (ever/never), alcohol consumption (ever/never), tumor site (oral cavity, oropharyngeal, hypooropharyngeal or laryngeal), stage (I and II vs. III and IV), sexual behaviors (lifetime number of sex partners, oral sex [ever/never], and lifetime number of oral sex partners), and HPV status. As controls were not assessed for sexual behavior, the stratified analysis by HPV status and sexual behavior was conducted in cases only. All *P* values were derived from two-sided statistical tests. R was used to conduct statistical analysis (version 3.0.2).

Results

A total of 2310 cases and 1915 controls had anthropometry data. The distribution of study participants by demographic, clinical, and epidemiological characteristics are summarized in **Table 1**. The majority of the cases (79.3%) and controls (70.1%) were at least 50 years of age at diagnosis, and the majority of the cases (70%) and controls (73.3%) were male. More cases than controls were underweight (2.8% vs. 0.8%; *P*< 0.0001). Of the cases, 76% had stage III or IV disease at presentation, 67.5% were current or former tobacco users, and 72% were current or former alcohol drinkers. Eighty-four percent of the cases were treated primarily with chemoradiotherapy, and 16% were treated primarily with surgery.

Overall, compared with normal weight, being overweight or obese was related to a decreased risk of SCCHN, while being underweight was associated with an increased risk of SCCHN

Table 2. Association between BMI and risk of SCCHN

BMI[a]	No. (%) of cases (*N* = 2310)	No. (%) of controls (*N* = 1915)	Adjusted OR (95% CI)[b]
Underweight	64 (2.8)	16 (0.8)	2.6 (1.5-4.7)
Normal[c]	661 (28.6)	425 (22.2)	1.0
Overweight	833 (36.1)	791 (41.3)	0.7 (0.6-0.8)
Obese	752 (32.6)	683 (35.7)	0.8 (0.7-0.9)

[a]Body mass index is a person's weight in kilograms divided by the square of the height in meters. [b]Unconditional logistic regression model adjusting for age, sex, race/ethnicity, smoking status, and alcohol use status. [c]Reference category.

after adjusting for age, gender, race/ethnicity, smoking, and alcohol consumption (**Table 2**). The risk of SCCHN was positively associated for underweight patients (OR, 2.6; 95% CI, 1.5-4.7) and negatively related with overweight patients (OR, 0.7; 95% CI, 0.6-0.8) or obese (OR, 0.8; 95% CI 0.7-0.9) compared to those having normal BMI.

Table 3 shows the relationship between BMI and SCCHN risk among cases stratified by smoking, alcohol, and tumor status. Table S1 summarizes the relationship between BMI and SCCHN risk among cases stratified by age, gender, stage, and race. After adjustment for age, sex, race/ethnicity, smoking status, alcohol consumption, tumor site, and stage, and an interaction term between smoking and alcohol, the association between low BMI and higher risk of SCCHN was stronger among patients at least 50 years of age (OR, 3.5; 95% CI, 1.5-7.9), males (OR, 3.4; 95% CI, 1.3-8.9), non-Hispanic whites (OR, 3.0; 95% CI, 1.5-5.8), ever drinkers (OR, 3.6; 95% CI, 1.5-8.5), individuals with hypopharyngeal or laryngeal tumor site (OR, 3.2; 95% CI, 1.4-7.6), and individuals who were both ever smokers and ever drinkers (OR, 4.0; 95% CI, 1.4-11.3). Analysis stratified by smoking and drinking showed a significant association between low BMI and risk of SCCHN (OR, 4.0; 95% CI, 1.4-11.3), implying an interaction effect of low BMI and smoking and drinking on the risk of SCCHN. Conversely, the associations between overweight and obesity and lower risk of SCCHN were stronger among elderly patients, men, patients with ethnicity other than non-Hispanic white, ever smokers, ever drinkers, patients with oral cavity tumors, patients with hypopharyngeal or laryngeal tumors, and patients with stage III or IV disease.

The presence of HPV antibodies, a marker of prior exposure to HPV, has been significantly associated with SCCOP risk [14-17]. **Table 4** shows the association between BMI and SCCOP risk, stratified by HPV16 serological status. Among patients with HPV seropositivity, the risk of SCCOP was increased in patients with higher BMI compared with normal-weight patients (overweight: OR, 5.4, 95% CI, 1.3-23.1; obese: OR, 2.4, 95% CI, 1.1-7.6). Patients with HPV seronegativity, on the other hand, have a lower risk of SCCOP with higher BMI than in normal-weight patients (overweight: OR, 0.5, 95% CI, 0.4-0.8; obese: OR, 0.6, 95% CI, 0.4-0.9) and a higher risk of SCCOP in underweight patients than in normal-weight patients (OR, 4.4, 95% CI, 1.1-17.2). Table S2 demonstrates that compared with normal weight there was a significant association between overweight or obese and HPV seropositivity in patients with SCCOP (overweight: OR, 1.7, 95% CI, 1.1-2.6; obese: OR, 2.3, 95% CI, 1.5-3.5).

Patients with SCCOP carry different risk-based profiles according to the tumor HPV status. Most notably, sexual activity is independently associated with HPV-positive SCCOP. Thus, we also evaluated the association between BMI and HPV serological status stratified by sexual practice among SCCOP patients. As shown in Table S3, among those with at least five lifetime sex partners, patients who had ever had oral sex, and patients with at least four lifetime oral sex partners, overweight and obese patients were approximately 1.5 to 2.5 times as likely as normal-weight patients to be HPV seropositive. We did not perform a similar analysis among patients with low BMI since data on sexual behaviors for most of these patients were not available. These results indicated that overall increased number of sex partners or ever having had oral sex may increase the risk of HPV seropositivity among SCCOP patients with overweight or obesity.

Discussion

In this large case-control study from a single cancer center, we evaluated whether pretreatment BMI was associated with risk of SCCHN

Table 3. Stratified analysis of association between BMI and risk of SCCHN among cases

Characteristic	Underweight Adjusted OR (95% CI)[a]	Normal[b] Adjusted OR (95% CI)[a]	Overweight Adjusted OR (95% CI)[a]	Obese Adjusted OR (95% CI)[a]
Smoking status		1.0		
Ever	2.5 (1.2-5.5)		0.6 (0.5-0.7)	0.6 (0.5-0.7)
Never	2.4 (0.9-6.1)	1.0	0.9 (0.7-1.2)	1.1 (0.8-1.4)
Alcohol use status				
Ever	3.6 (1.5-8.5)	1.0	0.6 (0.5-0.8)	0.7 (0.6-0.8)
Never	1.7 (0.7-4.0)	1.0	0.9 (0.7-1.2)	1.0 (0.7-1.3)
Tumor site				
Oral cavity	2.6 (1.3-5.0)	1.0	0.5 (0.4-0.6)	0.6 (0.5-0.7)
Oropharynx	2.8 (1.4-5.5)	1.0	0.8 (0.7-1.0)	0.9 (0.7-1.1)
Hypopharynx or larynx	3.2 (1.4-7.6)	1.0	0.6 (0.5-0.9)	0.6 (0.5-0.9)
Smoking and alcohol Ever smoker and ever drinker	4.0 (1.4-11.3)	1.0	0.5 (0.4-0.7)	0.6 (0.4-0.7)
Ever smoker and never drinker	0.7 (0.2-2.8)	1.0	0.6 (0.4-1.0)	0.7 (0.5-1.1)
Never smoker and ever drinker	1.1 (0.2-8.4)	1.0	0.8 (0.6-1.1)	1.0 (0.7-1.5)
Never smoker and never drinker	2.8 (1.0-8.3)	1.0	1.2 (0.8-1.7)	1.2 (0.8-1.7)

[a]Unconditional logistic regression model adjusting for age, sex, race/ethnicity, smoking status, alcohol use status, tumor site, stage, and an interaction term. [b]Reference category.

Table 4. Association between BMI and risk of SCCOP by HPV serostatus

HPV status	No. (%) of cases (*N* = 682)	No. (%) of controls (*N* = 745)	Underweight Adjusted OR (95% CI)	Normal[a] Adjusted OR (95% CI)	Overweight Adjusted OR (95% CI)	Obese Adjusted OR (95% CI)
E6 and E7 negative	280 (41.1)	728 (97.7)	4.4 (1.1-17.2)	1.0[c]	0.5 (0.4-0.8)	0.6 (0.4-0.9)
E6 and/or E7 positive	402 (58.9)	17 (2.3)	NC[b]	1.0	5.4 (1.3-23.1)	2.4 (1.1-7.6)
E6 Negative	260 (38.1)	739 (99.2)	4.5 (1.2-17.2)	1.0	0.6 (0.5-0.9)	0.8 (0.6-1.1)
E6 Positive	422 (61.9)	6 (0.8)	NC	1.0	5.4 (1.1-38.9)	10.8 (1.2-117.6)
E7 Negative	328 (48.1)	733 (98.4)	3.9 (1.2-15.1)	1.0	0.6 (0.4-0.8)	0.7 (0.5-1.0)
E7 Positive	354 (51.9)	12 (1.6)	NC	1.0	4.0 (1.0-25.8)	1.4 (1.1-6.1)

[a]Reference category. [b]NC: not calculable because of 0 cells (0 + controls).

[18]. Our results showed that being underweight was significantly associated to a higher risk of SCCHN and overweight or obesity was significantly associated with a reduced risk of SCCHN. Conversely, among those with HPV E6/7 seropositivity, overweight and obesity were related to a higher risk of SCCOP. Moreover, among the patients with SCCOP, overweight and obese patients had higher rates of HPV seropositivity than normal-weight patients in the subgroups that had higher numbers of lifetime sex partners, lifetime oral sex partners and those that reported ever having oral sex.

Several researchers have examined the association between obesity and risk of cancer. Although the results of these studies have been conflicting, the majority of previous literature indicated that higher BMI was a risk factor for breast cancer, colon cancer, esophageal adenocarcinoma, gallbladder cancer, and renal cancer [19]. However, there has been limited research regarding the association between BMI and risk of developing SCCHN. BMI is easy to measure in the clinic and convenient for use in research studies. A study comparing BMI with the risk of 22 specific cancers sites found that obesity had a protective effect on tumors at certain sites [20]; this phenomenon has been termed the “obesity paradox”. A possible explanation for this phenomenon is that increased nutritional reserves and higher body mass provides added advantage during the period of acute sickness. This could also explain why lower BMI group includes higher number of individuals suffering from disease, and therefore, are at a higher risk of mortality [21]. It has been suggested that different mecha-

nisms are associated with the impact of BMI on cancer risk in different cancers. The strong interaction between body structure and inflammation can influence metabolization, body weight, and immunity to tumor growth. Previous literature shows body composition analysis to be a superior tool in measuring adiposity, however, it is not yet a standard part of care in the hospital setting [21].

In the current study, we observed that low BMI was related with a higher risk of SCCHN, but the exact mechanism underlying this association remains unclear. It has been suggested that low BMI is closely related to low socioeconomic status and poor nutrition and may be associated with smoking [22]. Studies have shown that compared with overweight adults, adults with lower body weight have increased levels of 8-hydroxydeoxyguanosine, a biological marker indicating oxidative DNA damage, also persistent in smokers [23-25]. Similarly, DNA adducts, which indicate exposure to genotoxic aromatic compounds, metabolism, and repair, have also been seen to exist at increased levels in lower-weight adults than in overweight or obese adults [26]. These results may assist in understanding the link between leanness and higher SCCHN risk, particularly in smokers. Other proposed explanations for the association between leanness and higher SCCHN risk include differences between low-weight and normal-weight individuals in hormone metabolism, insulin-like growth factors, sex hormones, and adipokines [20]. Although our findings suggest that people who are average weight have a lower risk of SCCHN than those who are underweight (BMI <18 kg/m^2), the potential for reverse causality cannot be excluded, and in fact, Franceschi et al. found that SCCHN may lead to significant weight loss before it is diagnosed [18]. Thus, large prospective studies are necessary to better understand the relationship between underweight and SCCHN risk [20].

A previous case-control study concluded that obese HPV-seronegative cases had a lower risk of developing SCCHN (OR 0.5, 95% CI 0.32-0.70), but HPV-seropositive cases had an increased risk (OR 0.91, 95% CI 0.70-1.21) [27]. In the current study, we found a similar association between high BMI and HPV status on the risk of SCCOP. One potential explanation for this finding is that HPV-associated tumors are distinct from HPV-negative tumors and have different risk factors. HPV-positive SCCHN is associated with various sexual behavioral risk factors, including oral, vaginal, and anal sex. Higher exposure as estimated by younger age at sexual debut and the overall number of sexual partners is related to a dose-dependent risk of HPV-associated SCCHN [13, 28]. Our current study also found that a greater number of sexual partners over the course of their lives, and a greater number of oral sex partners were associated with an increased risk of HPV seropositivity among SCCOP patients who are overweight or obese.

There are several limitations to consider when interpreting this study. One important limitation is a lack of information on changes in BMI due to preclinical disease. BMI was measured close to disease diagnosis because of our case-control study design, which could have led to exposure misclassification. Self-reporting by study subjects could have also led to information bias. Smoking and alcohol use status were self-reported and hence susceptible to the same potential biases, and information was not collected regarding the quantity or duration of alcohol use. Finally, we are not able to adjust for nutrition and diet, which are potential confounding factors.

Despite the limitations, this study had considerable strengths. This study utilized a large data repository to assess associations, including information on HPV status based on serological testing. This study showed an interaction effect of BMI and smoking and alcohol use on the risk of SCCHN. Most notably, we identified an association between HPV E6/E7 seropositivity and increased BMI among SCCOP patients. These data provide opportunities for further investigation, including cancer screening and prevention.

Conclusion

Our findings provide strong evidence that BMI of 25 kg/m^2 or greater is associated with a lower risk of developing SCCHN. In addition to tobacco and alcohol use, BMI may be a modifiable risk factor for SCCHN. Strong associations between BMI and SCCHN risk were found across a number of stratifying variables, including HPV and sexual history. We identified an

association between HPV E6/E7 seropositivity and increased BMI among SCCOP patients. More research is required to better understand the biological processes that underpin these relationships between BMI, HPV, and SCCHN risk.

Acknowledgements

This research was accomplished within the Oropharynx Program at The University of Texas MD Anderson Cancer Center and funded in part through the Stiefel Oropharyngeal Research Fund.

Disclosure of conflict of interest

None.

Abbreviations

BMI, body mass index; SCCHN, squamous cell carcinoma of the head and neck; SCCOP, squamous cell carcinoma of the oropharynx; HPV, human papillomavirus; OR, odds ratio; CI, confidence interval.

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Table S1. Stratified analysis of association between BMI and risk of SCCHN among cases

Characteristic	Underweight Adjusted OR (95% CI)[a]	Normal[b] Adjusted OR (95% CI)[a]	Overweight Adjusted OR (95% CI)[a]	Obese Adjusted OR (95% CI)[a]
Age, years		1.0		
<50	1.7 (0.7-4.1)		0.7 (0.5-1.0)	0.8 (0.6-1.1)
≥50	23.5 (1.5-7.9)	1.0	0.7 (0.6-0.9)	0.8 (0.6-0.9)
Sex				
Male	3.4 (1.3-8.9)	1.0	0.7 (0.6-0.8)	0.7 (0.6-0.9)
Female	2.1 (1.0-4.5)	1.0	0.7 (0.5-1.0)	0.9 (0.6-1.2)
Race/ethnicity				
Non-Hispanic white	3.0 (1.5-5.8)	1.0	0.8 (0.6-0.9)	0.9 (0.7-1.1)
Other	1.2 (0.3-4.1)	1.0	0.4 (0.2-0.6)	0.4 (0.2-0.6)
Stage				
I/II	2.2 (1.0-4.8)	1.0	0.7 (0.5-0.8)	0.8 (0.6-1.0)
III/IV	2.8 (1.5-5.1)	1.0	0.7 (0.6-0.8)	0.8 (0.6-0.9)

[a]Unconditional logistic regression model adjusting for age, sex, race/ethnicity, smoking status, alcohol use status, tumor site, stage, and an interaction term. [b]Reference category.

Table S2. Association between BMI and HPV status in SCCOP among cases

	No. (%) E6/7(+) (N = 402)	No. (%) E6/7(-) (N = 280)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Underweight	3 (0.8)	9 (3.2)	0.4 (0.1-1.6)	0.5 (0.1-2.1)
Normal weight	67 (16.7)	83 (29.6)	1.0 (Ref)	1.0 (Ref)
Overweight	149 (37.1)	95 (33.9)	1.9 (1.3-2.9)	1.7 (1.1-2.6)
Obese	183 (45.5)	93 (33.2)	2.4 (1.6-3.7)	2.3 (1.5-3.5)

[a]Unconditional logistic regression model adjusting for age, sex, race/ethnicity, smoking status, alcohol use status, tumor site, stage, and an interaction term.

Table S3. Association between BMI and HPVE6/7 antibody serostatus among patients with SCCOP stratified by sexual behavior

Characteristic	No. (%) E6/7(+) (N = 479)	No. (%) E6/7(-) (N = 203)	Underweight Adjusted OR (95% CI)[a]	Normal[b] Adjusted OR (95% CI)[a]	Overweight Adjusted OR (95% CI)[a]	Obese Adjusted OR (95% CI)[a]
Lifetime number of sex partner				1.0		
<5	60 (28.6)	34 (44.2)	NC[b]		0.9 (0.3-3.0)	1.1 (0.3-3.4)
≥5	150 (71.4)	43 (55.8)	NC[b]	1.0	2.2 (1.1-5.5)	2.4 (1.0-5.9)
Missing	269	126				
Ever oral sex						
No	12 (4.8)	17 (18.5)	NC[b]	1.0	0.7 (0.1-6.5)	1.4 (0.1-13.7)
Yes	240 (95.2)	75 (81.5)	0.2 (0.0-2.3)	1.0	1.6 (1.2-3.2)	1.6 (1.1-3.2)
Missing	227	111				
Lifetime number of oral sex partners						
<4	91 (44.6)	42 (60.0)	NC[b]	1.0	2.0 (0.7-5.4)	1.7 (0.7-4.6)
≥4	113 (55.4)	28 (40.0)	0.4 (0.0-7.1)	1.0	1.9 (1.1-5.9)	2.1 (1.2-6.5)
Missing	275	133				

Reference category. [a]Unconditional logistic regression model adjusting for age, sex, race/ethnicity, smoking status, alcohol use status, tumor site, stage, and an interaction term. [b]NC: not calculable because of 0 cells (0 +controls).