A Population-based Case-Control Study of Marijuana Use and Head and Neck Squamous Cell Carcinoma

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Abstract

Background—Cannabinoids, constituents of marijuana smoke, have been recognized to have potential antitumor properties. However, the epidemiological evidence addressing the relationship between marijuana use and the induction of head and neck cancer (HNSCC) is inconsistent and conflicting.

Methods—Cases (n=434) were patients with incident disease from nine medical facilities in the Greater Boston, MA area between December 1999 and December 2003. Controls (n=547) were frequency-matched to cases on age (± 3 years), gender and town of residence, randomly selected from Massachusetts town books. A questionnaire was adopted to collect information on lifetime marijuana use (decade-specific exposures) and associations evaluated using unconditional logistic regression.

Results—After adjusting for potential confounders (including smoking and alcohol drinking), 10 to 20 years of marijuana use was associated with a significantly reduced risk of HNSCC (OR₁₀⁻<20 yrs vs never users=0.38, 95% CI=0.22–0.67). Among marijuana users moderate weekly use was associated with reduced risk (OR₀.₅⁻<1.₅ times vs. ≤0.₅ time =0.52, 95% CI=0.32–0.85). The magnitude of reduced risk was more pronounced for those who started use at an older age (OR₁₅⁻<20 yrs old versus never users =0.53, 95% CI=0.30–0.95; OR≥20 yrs old versus never users =0.39, 95% CI=0.17–0.90, P_{trend}<0.001). These inverse associations did not depend on HPV 16 antibody status. However, for the subjects who have the same level of smoking or alcohol drinking, we observed attenuated risk of HNSCC among those who use marijuana compared with those who do not.

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Conflict of Interest Statements
The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work to disclose.
Conclusion—Our study suggests that moderate marijuana use is associated with reduced risk of HNSCC.

Keywords
Cannabis; Head and Neck Cancer; prevention

Introduction
Marijuana (Cannabis sativa) contains more than 60 unique compounds known as cannabinoids. The major active cannabinoid in marijuana is Δ9-tetrahydrocannabinol (THC) 1. THC exerts a wide spectrum of biological effects by mimicking endogenous substances (the endocannabinoids anandamide and 2-arachidonoyl glycerol) that activate specific cell surface G-protein coupled cannabinoid receptors (CB1 and CB2)2. CB2 receptors are highly expressed on immune cells and are believed to play an important role in immunomodulation by regulating cell migration and cytokine release 3, whereas CB1 receptors are mainly expressed in the central nervous system and involved in inhibition of the release of neurotransmitters4. Both cannabinoid receptors are involved in transmission of signals via inhibiton of adenylyl cyclase and mitogen-activated protein kinases (MAPK)5. Both of these signaling pathways are active in chronic inflammatory conditions as well as in malignant diseases and, therefore, cannabinoid receptors and the endocannabinoid system have been recently recognized as potential therapeutic targets in many conditions 2-4.

The association between marijuana use (and its constituent cannabinoids) and cancer has received considerable attention in the recent scientific literature. Experimental data have demonstrated that cannabinoids are inhibitors of cancer cell invasion and migration 6-8, and these compounds are also known to have antiproliferative and antiangiogenic effects on glioma 9. Further, additional work demonstrates that cannabinoids are potent anti-inflammatory agents 10-11. It is also known that the CB1 receptor (encoded by CNR1) is expressed in the mouse and human aerodigestive tract 12 and animal models now show that alteration of cannabinoid levels or inactivation of the cannabinoid receptor complex can contribute to intestinal tumor growth 13, 14. Finally, when breast cancer cells were treated with cannabinoids, aberrant signaling cascades associated with the abrogation of apoptosis were inhibited, indicating that cannabinoids are potentially potent therapeutics 15.

Concomitantly, the epidemiologic evidence addressing the relationship between marijuana use and the induction of cancers, especially head and neck cancer, is inconsistent and conflicting. An early epidemiological study reported that marijuana use was associated with an elevated risk for head and neck cancer 16. However, more recent studies have failed to confirm the association of marijuana use with an increased head and neck cancer risk 17-22. In fact, many of these studies reported non-significant protective estimates of effect, consistent with a possible anticarcinogenic action of cannabinoids. A recent epidemiologic review raised the need for additional, well conducted, large studies to clarify the nature of the association of marijuana use with the risk of cancer, especially head and neck cancer 23. In order to further elucidate the association between marijuana use and head neck cancer risk, we assessed marijuana use in detail in a population-based case-control study.

Materials and Methods

Study subjects
Cases in this study were head and neck squamous cell carcinoma (HNSCC) patients identified from head and neck clinics and departments of otolaryngology or radiation oncology at nine medical facilities in Greater Boston, MA between December 1999 and December 2003 (for
further details see 24–26). HNSCC cases included diagnosis codes 141–146, 148, 149, and 161 according to International Classification of Disease, Ninth Revision (ICD-9). Eligible cases were residents in the study area aged 18 years or older and with a pathologically confirmed diagnosis of HNSCC no more than 6 months before the time of patient contact. Cases with recurrent disease were excluded. The cancer registry was queried to insure that all eligible cases in the area were identified. Controls were frequency-matched to cases on age (± 3 years), gender, and town of residence, identified from Massachusetts town books using random selection (for further details see 24–26). Study protocols and materials for recruitment of cases and controls were approved by the Institutional Review Boards at the nine medical facilities and Brown University. Written informed consent was obtained from all study subjects.

Data collection

A self-administered questionnaire was used to collect information about demographic characteristics and the standard risk factors for HNSCC, including medical history, family history of cancer, detailed smoking and drinking habits, detailed marijuana use history, occupational history and residency history. Questionnaires were distributed to cases during an initial clinic visit and to controls by mail. All the subject responses were reviewed by study personnel and research coordinators during in-person visits with cases or controls. To elicit the history of marijuana use, subjects were first asked to report whether or not they ever used marijuana. The subjects who reported having ever used marijuana were asked to specify their ages at starting and stopping using marijuana, frequency, modes and amount of use as well as whether they inhaled when smoking for 8 time periods in their life (ages 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+). For the frequency of use, subjects reported how many times they smoked in a typical week during each smoking period by selecting from multiple choice answers (<1 per week, 1–2 per week, 3–6 per week, 1 per day, 2–4 per day, 5–7 per day, 8–10 per day, and 11+ per day). Subjects were asked how they smoked marijuana during each smoking period by selecting from multiple choice answers (rolled (joint), pipe, and water pipe). In addition, subjects were asked how many ounces of marijuana they used per week during the smoking years specified. History of smoking and alcohol consumption was collected in a similar, decade-specific fashion.

The HPV16 serologic status of case and control subjects was ascertained as described previously 24, 25. Venous blood samples were obtained from cases and controls at enrollment. Serum was separated from plasma within 24 hours of collection and stored at -80°C. The HPV Competitive Luminex Immunoassay was used to determine presence of antibodies to the L1 protein of HPV16. Positive and negative controls were used for quality control, and all samples were tested in duplicate.

Exposure Measurement

Subjects’ marijuana use status was classified as never, current and former use. Subjects who indicated that they had never used marijuana were considered never users. Those who reported that they had ever used marijuana were classified as current or former users based upon the years since last use, which were determined by the difference between current age and the maximum age of stopping marijuana use. The age at starting marijuana use was indicated by the minimum age of starting marijuana use during lifetime.

To determine the duration of marijuana use in lifetime, we first calculated the number of years use during each decade of life, which was expressed as the difference between the age at starting marijuana use and the age at stopping marijuana use plus one, and then summed all the number of years across all smoking age periods. Similarly, to determine the cumulative marijuana use in lifetime, the total number of times (times/week*years) and total number of ounces (ounces/
(times/week) of marijuana use were calculated. In order to determine the overall total number of times of use, the midpoint of each category of times per week was first multiplied by the duration of use during that smoking years specified, and then the products were summed. In order to estimate the total number of ounces used, the midpoint of ounces per week for each category was first multiplied by the duration of use in each smoking period, and then the products were summed. The lifetime average frequency of marijuana use (times/week) were measured by total number of times dividing by the total number of years the subject reported smoking. Similarly, the lifetime average amount of marijuana use (ounces/week) was calculated by total number of ounces dividing by the total number of years reported.

In order to explore the dose-response for HNSCC risk, we employed cut-off points derived from the combined distribution in both cases and controls among ever users. Subjects who reported never using marijuana served as reference group except for the estimates of average frequency and average amount of marijuana use, in which the combinations of the lowest quartiles and never users served as reference group in order to maximize the statistical power. The remaining categories were established by the quartiles based on the joint distributions of marijuana use in both cases and controls.

**Statistical analysis**

To describe the distribution of demographic variables and explore the potential confounders, t-tests were used for the continuous variables and Chi-square tests were used for categorical variables (see Table 1). Unconditional logistic regression was appropriate for this frequency-matched case-control study to evaluate the association between marijuana use and the risk of HNSCC. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with and without adjustment for the potential confounders. Besides age and gender, covariates such as race, education, HPV16 serology, family history of cancer, smoking pack-years, and average alcohol drinks per week were included for adjustment. Test for trend was performed by treating the ordinal variables as continuous variables to evaluate the dose-response of marijuana use for the risk of HNSCC. To determine the effect measure modification between marijuana use and HPV16 serology, we estimated stratum-specific ORs associated with marijuana use by HPV16 antibody status (negative and positive) and joint ORs for marijuana use and each of these variables. To assess the joint effects for marijuana use with smoking or alcohol drinking or both smoking and drinking, we selected the lowest exposure category for the two risk factors combined as the reference group and included the remaining combined categories as indicator variables. We also examined the multiplicative association using likelihood ratio tests to fit the models with and without the interaction terms (a cross product of two ordinal variables). Additionally, polytomous logistic regression was adopted to examine the association between marijuana use and the risk of HNSCC by the tumor location. ORs and CIs were also calculated with and without adjustment for the potential confounders. Tumor sites were classified as oral cavity, pharynx and larynx, as described by the American Joint Committee on Cancer (AJCC). Control group served as the reference group when processing polytomous logistic regression analysis. All tests were performed in SAS version 9.13, and all reported P values are based on two-sided tests with 0.05 as significance level.

**Results**

There were 1280 eligible subjects enrolled in this study. Details concerning participation rates and reasons for refusal were described previously. Of these 1280 subjects, 299 were excluded due to unavailable HPV 16 detection (n=248), or missing information regarding marijuana use (n=51). Among the 981 subjects, 434 were cases with HNSCC (160 oral, 190 pharynx and 84 larynx) and 547 were control subjects. The distribution of characteristics for cases and controls is presented in Table 1. Cases and controls had similar distribution of age, gender and race.
The mean age of the participants in both groups was approximately 60. Most subjects were males (73%) and Caucasian (91%). Cases were more likely to report lower education compared with controls ($P<0.001$). There was no significant difference between cases and controls in family history of cancers, family history of HNSCC or first-degree relatives with cancer. As expected, cases were more likely to smoke or drink heavily ($P<0.001$). Also, we observed a greater prevalence of HPV 16 seropositivity in cases than in controls ($P<0.001$).

Table 2 shows the association of HNSCC with marijuana use. Current users had a decreased cancer risk of borderline statistical significance before adjusting for known risk factors. However, after adjusting for known risk factors (including age, gender, race, education, family history of cancer, HPV 16, smoking pack-years and average drinks of alcohol per week), the association between marijuana use and HNSCC was statistically significant (adjusted OR$_{\text{current vs. never users}}=0.52$, 95% CI=0.34–0.80, $P_{\text{trend}}<0.001$). We observed that participants who reported 10 to 20 years of marijuana use had an inverse association with the risk of HNSCC (adjusted OR$_{10-<20 \text{ yrs vs. never users}}=0.38$, 95% CI=0.22–0.67), as did the participants who reported marijuana use 0.5 to 1.5 times per week (adjusted OR$_{0.5-<1.5 \text{ times vs. }<0.5 \text{ time}}=0.52$, 95% CI=0.32–0.85). The estimates of moderate lifetime use were observed to decrease the risk of HNSCC (adjusted OR$_{5-<15 \text{ versus never users}}=0.36$, 95% CI=0.18–0.69). Among former users, those who used in the last 2 years had 43% lower risk of HNSCC compared to never users (adjusted OR$_{<2 \text{ yrs versus never users}}=0.57$, 95% CI=0.38–0.86; $P_{\text{trend}}=0.01$). The magnitude of decreased risk of HNSCC was more pronounced for those who started at an older age (adjusted OR$_{15-<20 \text{ yrs old versus never users}}=0.53$, 95% CI=0.30–0.95; adjusted OR$_{>20 \text{ yrs old versus never users}}=0.39$, 95% CI=0.17–0.90, $P_{\text{trend}}<0.001$). No significant association was found for amount of marijuana use and HNSCC.

To investigate the role of HPV 16 in the association between marijuana use and HNSCC, we performed stratified analysis and joint effects analysis (Table 3). The association of HNSCC and marijuana use remained unchanged when stratified by HPV 16 antibody status. Although the inverse association did not reach statistical significance in the HPV 16 seropositive strata, we observed similar point estimates in both HPV 16 negative and positive strata. No departure from multiplicative association between marijuana use and HPV 16 antibody status on the risk of HNSCC ($P_{\text{interaction}}=0.918$) was detected.

We next performed a joint-effects analysis to investigate the association between marijuana use and HNSCC by level of smoking or alcohol consumption (Table 4). A decreased risk was observed among the subjects with ever marijuana use and less than 20 pack-years smoking (OR=0.51, 95% CI=0.27–0.96), but compared with never marijuana users and never tobacco smokers, increased risk was found among ever marijuana users and heavy smokers (OR=2.20, 95% CI=1.30–3.74), though this risk was >20% lower than that observed in heavy smoking never marijuana users (OR=2.85, 95% CI=1.86, 4.36). Similar inverse associations were obtained for the joint effects of marijuana use and alcohol drinking amongst the lowest drinkers (OR=0.56, 95% CI=0.32–0.96), but also attenuation of risk amongst the heaviest drinkers. We subsequently combined average alcohol drinks and pack-years of tobacco smoking together and observed nonsignificant reduced HNSCC risk among ever marijuana users with moderate tobacco smoking (<20 pack-years) regardless of alcohol drinking. As expected, the combination of either smoking or drinking or both smoking and drinking among never marijuana users increased the risk of developing HNSCC. Departure from multiplicative association of tobacco smoking, alcohol drinking and marijuana use on the risk of HNSCC was detected ($P_{\text{interaction}}=0.006$).

In order to examine whether the associations between marijuana use and HNSCC varied by specific tumor sites, polytomous logistic regression was used and results suggested no difference across tumor sites for the association between marijuana use and HNSCC.
Larynx: current versus never $=0.44$, 95% CI=$0.21–0.96$; OR Pharynx: current versus never $=0.63$, 95% CI=$0.37–1.08$; OR Oral: current versus never $=0.47$, 95% CI=$0.27–0.82$), although there may be the suggestion of slightly more protection in the oral cavity. We did not observe any association by stage at diagnosis (data not shown). Additionally, we had little power to investigate modes of marijuana use and the risk of HNSCC because 93.41% of users adopted rolled (joint) use while only 24.18 % indicated that they had used a pipe and 17.58 % a water pipe. We also examined the association between marijuana use and HNSCC among the limited number of nonsmokers and detected no significant associations (results not shown).

### Discussion

We found that moderate marijuana use was significantly associated with reduced risk of HNSCC. This association was consistent across different measures of marijuana use (marijuana use status, duration, and frequency of use). Diminished risk of HNSCC did not differ across tumor sites, or by HPV 16 antibody status. Further, we observed that marijuana use modified the interaction between alcohol and tobacco, resulting in a decreased HNSCC risk among moderate smokers and light drinkers, and attenuated risk amongst the heaviest smokers and drinkers.

Our observation that low-dose marijuana use was associated with a lower risk of HNSCC is consistent with several studies with strikingly similar point estimates (Table 5). The previous studies may in fact have observed precisely the same associations as we have reported, but these studies were not sufficiently powered to reach statistical significance. These several lines of evidence are consistent with our observation that moderate marijuana use decreases the risk of HNSCC, in contrast to the results of the first epidemiological study by Zhang et al 16, who detected a 2–3 fold risk of HNSCC for marijuana users. The study by Zhang et al selected blood donors as controls, who may have a lower prevalence of marijuana use.

In addition to increased statistical power, our study may have had more statistical acuity from improved exposure assessment. Another possible explanation of the discrepancies could be attributed to potential confounders. In our study, besides the common confounders (e.g. age, gender, race, education, smoking and alcohol drinking), we also adjusted for family history of cancer and HPV 16 antibody status. HPV16 prevalence was shown to be significantly different between cases and controls. Therefore, the potential inverse association between marijuana use and HNSCC had been raised although not verified. Our study confirmed this relationship and provided some additional clues for further study.

Numerous recent studies have demonstrated that cannabinoids have antitumor effects, including activity on the cell cycle and cell growth arrest as well as acting upon the promotion of apoptosis, angiogenesis and cellular migration 4, 5. There is urgent interest in using cannabinoids as therapeutic agents in glioma28. Indeed, mouse models now very dramatically show that these agents are potent inhibitors of tumor growth in the gastrointestinal tract 13, 14. All of these data together demonstrate that cannabinoids potently act to alter cellular signaling. This action of cannabinoids is mediated through the CB1 and CB2 receptors and hence almost certain to be cell and tissue-specific. There is a definite need for further research into the tissue-specific action of cannabinoids in mouse models and in humans, specifically seeking to understand the possible differences in mechanistic action of these compounds in distinct tissues.

HPV 16 is a strong risk factor of HNSCC. Alcohol or tobacco use was found to have no association with HPV-16-positive pharyngeal cancer while positive association was observed in HPV-16-negative pharyngeal cancer 24. In contrast, our stratification analysis showed an independent relationship between marijuana use and HNSCC regardless of HPV 16 antibody
status. No departure from multiplicative association was observed between marijuana use and HPV 16 antibody status in the risk of HNSCC. Although nonsignificant associations were found in HPV 16 positive HNSCC resulting from small sample size, the similar point estimates of ORs in both positive and negative HPV 16 groups, to some extent, established a decreased risk for HNSCC that did not depend on HPV 16 antibody status. This is inconsistent with the finding by Gillison, et al. 22, in which HPV-16-positive HNSCC was exhibited to be positively associated with marijuana use. However, these investigators studied a very limited number of HPV 16 positive cases.

Smoking and alcohol drinking have been known as strong risk factors for HNSCC, and have been well established to interact greater than multiplicatively in causing HNSCC 24, 29, 30. They were also shown to be strong predictors of marijuana use, particularly when more frequent and higher rates of use were assessed 31. In our study, we observed positive associations between marijuana use and tobacco smoking or alcohol drinking ($r_{\text{marijuana vs smoking}}=0.35$; $r_{\text{marijuana vs alcohol}}=0.34, P<0.001$). In order to examine whether the association between marijuana use and HNSCC differed by different levels of smoking or alcohol drinking, we examined the effect measure modification of marijuana use associated with either smoking or alcohol and both. Our observation suggested that the risk of HNSCC was attenuated among those smokers or alcohol drinkers who ever used marijuana. When combined with alcohol and smoking together, the magnitude of the association varied little among moderate smokers regardless of alcohol drinking. This finding suggested a certain degree of departure from multiplicative association between marijuana use and smoking, or both smoking and alcohol drinking on the induction of HNSCC. Further, although we did not observe an association between marijuana use and HNSCC among non-smokers, this may be due to the limited number of non-smokers available for this study. In contrast to our study, previous studies generally considered smoking and alcohol drinking as potential confounders rather than as measures of effect modification.

Perhaps the main strength of our study is the fact that marijuana use was measured based upon decade-specific exposures, providing more precise details of marijuana use and reduced misclassification of exposure. The other major potential covariates, smoking and alcohol drinking were also similarly assessed (using decade-specific reporting). Our data indicated that among ever users of marijuana, marijuana use varied greatly over time, more so than did cigarette smoke or alcohol drinking among smokers or alcohol drinkers. It is possible that the variability of marijuana use as well as cigarette smoke and alcohol drinking over time is what makes the more crude methods from other studies insufficient to reach statistically significant results. Further, ours is a population-based study with a sample size sufficient to assess moderate associations. Finally, we were able to examine the joint effects and interaction between both HPV 16, smoking or alcohol drinking, and marijuana use on the risk of HNSCC, which has been addressed by few studies.

Of course, missing data is a concern in this study although we made a great effort to check the missing data and updated the dataset, especially when adjusting different potential confounders or when analyzing the joint effects between marijuana use and other covariates. However, missing data is most likely to give rise to unstable results only if the data are missing in a biased fashion. Moreover, missing data can result in small sample size because the records with missing data were excluded.

Finally, we cannot rid the study of all potential selection bias, information bias or possible residual confounding. Lower participation rate for controls (47%) and cases (88%) 24 may introduce selection bias since we were unable to evaluate whether there was no difference in marijuana use between participants and nonparticipants. However, we did observe comparable descriptive characteristics between included and excluded subjects in this study. (On the other
hand, given the illegal use of marijuana in US, subjects may report their marijuana use conservatively. This conservative answer may lead to information bias (reporting bias or recall bias). If this bias introduced differently in cases and controls, differential misclassification of marijuana use may be present and the association may be underestimated or overestimated. However, subjects were blind to the study hypothesis. Non-differential misclassification was more likely to appear in this study, which may underestimate the association for dichotomous variables.) Further, the questionnaire was given to cases in clinic but by mail to controls, and cases with direct contact with health professionals might feel uncomfortable to report the marijuana use. However, cases and controls had their questionnaires reviewed in person by a research assistant in an area away from health care providers or friends and family. It was unlikely that the different settings meaningfully altered the subjects’ responses. Although it is not impossible, we believe that this differential bias is very small and most likely had little impact on our observed results. Lastly, we could not exclude the residual confounding that resulted from the broad classification of exposures or other covariates (especially smoking and alcohol) and unmeasured variables as well as missing data.

Our study suggests that moderate marijuana use is associated with reduced risk of HNSCC. However, marijuana is an entry level drug and can be associated with later use of more serious addictive drugs, as well as other risky behaviors. Any policy regarding marijuana use should take these considerations and should not be made based upon one study’s results. Despite our results being consistent with the point estimates from other studies, there remains a need for this inverse association to be confirmed by further work, especially in studies with large sample sizes.

Acknowledgments

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References

31. Bailey, SR. Cigarette smoking and alcohol use as predictors of marijuana use in adolescence and young adulthood: Results from the 2002 and 2003 National Survey on Drug Use and Health [Dissertations & Theses]. Purdue University; 2006.
Table 1

Distribution of descriptive characteristics for cases and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=434)</th>
<th>Controls (n=547)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>59.68±11.41</td>
<td>60.99±11.44</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Female</td>
<td>114 (26.27)</td>
<td>147 (26.87)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>320 (73.73)</td>
<td>400 (73.13)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>Caucasian</td>
<td>389 (90.68)</td>
<td>499 (91.22)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>15 (3.5)</td>
<td>19 (3.47)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>25 (5.83)</td>
<td>29 (5.3)</td>
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</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lower than high school</td>
<td>76 (17.59)</td>
<td>43 (7.88)</td>
<td></td>
</tr>
<tr>
<td>High school or equivalence</td>
<td>172 (39.81)</td>
<td>203 (37.18)</td>
<td></td>
</tr>
<tr>
<td>College or higher</td>
<td>184 (42.59)</td>
<td>300 (54.95)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>1</td>
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</tr>
<tr>
<td>Family history of cancer</td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>345 (79.49)</td>
<td>440 (80.44)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>89 (20.51)</td>
<td>107 (19.56)</td>
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<tr>
<td>Family history of HNSCC</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>422 (97.24)</td>
<td>535 (97.81)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (2.76)</td>
<td>12 (2.19)</td>
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<tr>
<td>First-degree relative with cancer</td>
<td></td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>No</td>
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<td>453 (82.82)</td>
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<tr>
<td>1–2</td>
<td>61 (14.06)</td>
<td>79 (14.44)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>13 (3)</td>
<td>15 (2.74)</td>
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<tr>
<td>Pack-years of tobacco use</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<td>None</td>
<td>78 (17.97)</td>
<td>182 (33.27)</td>
<td></td>
</tr>
<tr>
<td>&gt;0 to &lt;20</td>
<td>83 (19.12)</td>
<td>152 (27.79)</td>
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<td>20 to &lt;45</td>
<td>116 (26.73)</td>
<td>121 (22.12)</td>
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<tr>
<td>≥45</td>
<td>157 (36.18)</td>
<td>92 (16.82)</td>
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<td>Alcohol consumption, average drinks per week</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;3</td>
<td>70 (16.43)</td>
<td>139 (25.6)</td>
<td></td>
</tr>
<tr>
<td>3 to &gt;8</td>
<td>89 (20.89)</td>
<td>176 (32.41)</td>
<td></td>
</tr>
<tr>
<td>8 to &lt;25</td>
<td>101 (23.71)</td>
<td>147 (27.07)</td>
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<tr>
<td>≥25</td>
<td>166 (38.97)</td>
<td>81 (14.92)</td>
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<td>Missing</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>HPV 16</td>
<td></td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>300 (69.12)</td>
<td>489 (89.4)</td>
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<td>Characteristic</td>
<td>Cases (n=434)</td>
<td>Controls (n=547)</td>
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<td>Tumor sites</td>
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<td>Pharynx</td>
<td>190 (43.78)</td>
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<td>Larynx</td>
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### Table 2

Association of head and neck squamous cell carcinoma with marijuana use

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case n=434(%)</th>
<th>Controls n=547 (%)</th>
<th>OR1</th>
<th>95% CI</th>
<th>OR2</th>
<th>95% CI</th>
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<td>396 (72.39)</td>
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<tr>
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<td>36 (8.29)</td>
<td>41 (7.50)</td>
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<td>396 (72.53)</td>
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<tr>
<td>&gt;0 to &lt;10</td>
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<td>59 (10.79)</td>
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<td>0.48 - 1.17</td>
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<td>55 (10.05)</td>
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<td>37 (6.76)</td>
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<td><strong>Average frequency of marijuana use per week (Times)</strong></td>
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<td>396 (72.53)</td>
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<td>1.00</td>
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<tr>
<td>0.5 to &lt;1.5</td>
<td>43 (9.93)</td>
<td>71 (13.00)</td>
<td>0.65</td>
<td>0.42 - 1.00</td>
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<td>0.32 - 0.85</td>
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<td>40 (7.33)</td>
<td>1.06</td>
<td>0.64 - 1.73</td>
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<td>0.31 - 0.99</td>
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<td>0.01</td>
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<td><strong>Total numbers of marijuana use in lifetime (Times/week * years)</strong></td>
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<td>396 (72.53)</td>
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<td>&gt;0 to &lt;5</td>
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<td>0.44 - 1.30</td>
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<td>0.34 - 1.17</td>
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<td>42 (7.69)</td>
<td>0.46*</td>
<td>0.25 - 0.83</td>
<td>0.36*</td>
<td>0.18 - 0.69</td>
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<td>15 to &lt;90</td>
<td>32 (7.39)</td>
<td>43 (7.88)</td>
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<td>0.47 - 1.30</td>
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<td>0.30 - 0.94</td>
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<td>28 (5.13)</td>
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<td>0.85 - 2.49</td>
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<td>0.41 - 1.47</td>
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<td>Variables</td>
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<td>Controls n=547 (%)</td>
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<td>OR² 95% CI</td>
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<td>-------------------</td>
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<tr>
<td><em><em>Total amount of marijuana use in lifetime (Ounces/week</em> years)</em>*</td>
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<tr>
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<td>29 (5.63)</td>
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<td>3 to &lt;7.5</td>
<td>24 (5.80)</td>
<td>33 (8.70)</td>
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<td>0.50</td>
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</tr>
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<tr>
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<td>0.08</td>
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<td><strong>Average amount of marijuana use per week (Ounces)</strong></td>
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<td>&lt;3/32</td>
<td>334 (80.68)</td>
<td>430 (79.46)</td>
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<td>3/32 to &lt;1/4</td>
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<td>32 (6.21)</td>
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<td>0.51</td>
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<tr>
<td>1/4 to &lt;3/4</td>
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<tr>
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<td>32</td>
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<td><strong>P Trend</strong></td>
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<td>0.58</td>
<td>0.22</td>
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<td><strong>Years since last marijuana use</strong></td>
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<td>318 (73.27)</td>
<td>396 (72.39)</td>
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<td>1.00</td>
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</tr>
<tr>
<td>&lt;2</td>
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<td>117 (21.39)</td>
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<td>2 to &lt;12</td>
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<td>9 (1.65)</td>
<td>1.11</td>
<td>0.73</td>
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<td>12 to &lt;22</td>
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<td>16 (2.93)</td>
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<tr>
<td>≥22</td>
<td>9 (2.07)</td>
<td>9 (1.65)</td>
<td>1.07</td>
<td>0.68</td>
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</tr>
<tr>
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<td>0.01</td>
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<td>396 (72.39)</td>
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<td>1.00</td>
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</tr>
<tr>
<td>10 to &lt;15</td>
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<td>78 (14.26)</td>
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<td>15 to &lt;20</td>
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<td>50 (9.10)</td>
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<td>0.48</td>
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<td>23 (4.20)</td>
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<td>0.24</td>
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<tr>
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<td>0.00</td>
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</table>

OR¹ adjusted for age and gender

OR² adjusted for age, gender, race, education, family history of cancer, HPV-16, smoking (packyears) and average drinks of alcohol per week.
Table 3
Association of head and neck squamous cell carcinoma with marijuana use by HPV 16 antibody status

<table>
<thead>
<tr>
<th>Variables</th>
<th>HPV16 Case n=434 (%)</th>
<th>Controls n=547 (%)</th>
<th>Stratified OR</th>
<th>95% CI</th>
<th>Joint effects OR²</th>
<th>95% CI</th>
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<td>230 (76.67)</td>
<td>361 (73.82)</td>
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<td>-</td>
<td>1.00</td>
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<tr>
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<td>21 (7.00)</td>
<td>35 (7.16)</td>
<td>0.62</td>
<td>0.31</td>
<td>1.24</td>
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<td>93 (19.02)</td>
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<td>0.29</td>
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<td>0.51</td>
</tr>
<tr>
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<tr>
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<td>35 (60.34)</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>4.71</td>
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<td>361 (73.98)</td>
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<td>-</td>
<td>-</td>
<td>1.00</td>
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<td>0.5 to &lt;1.5</td>
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<td>59 (12.09)</td>
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<td>34 (6.97)</td>
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<td>34 (6.97)</td>
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<td>35 (60.34)</td>
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<td>-</td>
<td>-</td>
<td>4.72</td>
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<td>0.5 to &lt;1.5</td>
<td>18 (13.53)</td>
<td>12 (20.69)</td>
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<td>0.18</td>
<td>1.33</td>
<td>2.74</td>
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<td>5 (8.62)</td>
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<td>0.22</td>
<td>3.16</td>
<td>3.43</td>
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<td>6 (10.34)</td>
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<td>1.95</td>
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</table>

OR¹ stratified by HPV 16 antibody status

OR² joint effect with HPV 16 antibody status

All ORs were adjusted for age, gender, education, race, smoking (packyears), and average drinks of alcohol
Table 4
Joint effects of marijuana use and smoking or alcohol consumption with head and neck squamous cell carcinoma

<table>
<thead>
<tr>
<th>Variables</th>
<th>Marijuana use Status</th>
<th>OR(95% CI)</th>
<th>Cases/Controls</th>
<th>OR(95% CI)</th>
<th>Cases/Controls</th>
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<td>Never</td>
<td>Ever</td>
<td>Never</td>
<td>Ever</td>
<td></td>
</tr>
<tr>
<td>Smoking (Pack-years)</td>
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</tr>
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<td>Never</td>
<td>1.00</td>
<td>0.48 (0.22–1.06)</td>
<td>66/141</td>
<td>0.22 (0.22–1.06)</td>
<td>12/41</td>
</tr>
<tr>
<td>&lt;20</td>
<td>1.40 (0.86–2.27)</td>
<td>0.51 (0.27–0.96)</td>
<td>56/96</td>
<td>0.27 (0.27–0.96)</td>
<td>27/56</td>
</tr>
<tr>
<td>&gt;=20</td>
<td>2.85 (1.86–4.36)</td>
<td>2.20 (1.30–3.74)</td>
<td>196/159</td>
<td>1.30 (1.30–3.74)</td>
<td>77/54</td>
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<td>Alcohol drinks/per week</td>
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<td>0.56 (0.32–0.96)</td>
<td>124/242</td>
<td>0.32 (0.32–0.96)</td>
<td>35/73</td>
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<td>&gt;=8</td>
<td>2.01 (1.41–2.86)</td>
<td>1.21 (0.76–1.92)</td>
<td>186/150</td>
<td>0.76 (0.76–1.92)</td>
<td>81/78</td>
</tr>
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<td>Smoking &amp; Alcohol</td>
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<td></td>
</tr>
<tr>
<td>Never &amp; &lt;8</td>
<td>1.00</td>
<td>0.60 (0.23–1.58)</td>
<td>42/102</td>
<td>0.23 (0.23–1.58)</td>
<td>7/26</td>
</tr>
<tr>
<td>Never &amp; &gt;=8</td>
<td>1.96 (0.96–3.99)</td>
<td>0.71 (0.22–2.31)</td>
<td>21/35</td>
<td>0.22 (0.22–2.31)</td>
<td>5/15</td>
</tr>
<tr>
<td>&lt;20 &amp; &lt;8</td>
<td>1.70 (0.93–3.09)</td>
<td>0.57 (0.25–1.32)</td>
<td>33/62</td>
<td>0.25 (0.25–1.32)</td>
<td>13/31</td>
</tr>
<tr>
<td>&lt;20 &amp; &gt;=8</td>
<td>2.06 (1.02–4.15)</td>
<td>0.90 (0.39–2.07)</td>
<td>22/34</td>
<td>0.39 (0.39–2.07)</td>
<td>14/25</td>
</tr>
<tr>
<td>&gt;=20 &amp; &lt;8</td>
<td>2.35 (1.34–4.14)</td>
<td>1.79 (0.74–4.31)</td>
<td>49/78</td>
<td>0.74 (0.74–4.31)</td>
<td>15/16</td>
</tr>
<tr>
<td>&gt;=20 &amp; &gt;=8</td>
<td>6.38 (3.76–10.83)</td>
<td>4.75 (2.58–8.76)</td>
<td>143/81</td>
<td>2.58 (2.58–8.76)</td>
<td>62/38</td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
</tbody>
</table>

Model1: adjusted for age, gender, race, education, family history of cancer, HPV-16, and average drinks of alcohol
Model2: adjusted for age, gender, race, education, family history of cancer, HPV-16, and packyears of smoking
Model3: adjusted for age, gender, race, education, family history of cancer, HPV-16
Table 5

Case-controls studies on the association of marijuana use and head and neck cancer

<table>
<thead>
<tr>
<th>Characteristics of cases and controls</th>
<th>Prevalence of marijuana use</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ever use</td>
<td>Times used/week</td>
</tr>
<tr>
<td></td>
<td>0.9(0.6-1.3)</td>
<td>&lt;1 yr</td>
</tr>
<tr>
<td>19 Cases:407, OSCC 25.6%</td>
<td>Never</td>
<td>1.0 (0.6-1.8)</td>
</tr>
<tr>
<td>Controls: 615</td>
<td>Never</td>
<td>&lt;1 yr</td>
</tr>
<tr>
<td></td>
<td>1 yr</td>
<td>0.2(0.1-0.7)</td>
</tr>
<tr>
<td></td>
<td>&lt;1 yr</td>
<td>1.3(0.6-2.6)</td>
</tr>
<tr>
<td>18 Cases:116, OSCC 15.13%</td>
<td>6-15 yrs</td>
<td>0.7(0.4-1.4)</td>
</tr>
<tr>
<td>Controls: 207</td>
<td>&gt;15 yrs</td>
<td>1.2(0.6-2.2)</td>
</tr>
<tr>
<td>20 Oral: 188(62%)</td>
<td>188(62%)</td>
<td>Oral cancer</td>
</tr>
<tr>
<td>20 Oral: 188(62%)</td>
<td>188(62%)</td>
<td>Pharyngeal cancer</td>
</tr>
<tr>
<td>40(40%)</td>
<td>51(57%)</td>
<td>1.1 (0.74-1.5)</td>
</tr>
<tr>
<td>Oral cancer</td>
<td>10 to &lt;30 jnt-yrs</td>
<td>0.92 (0.48-1.7)</td>
</tr>
<tr>
<td>Oral cancer</td>
<td>≥60 jnt-yrs</td>
<td>0.88 (0.38-2.0)</td>
</tr>
<tr>
<td>Laryngeal cancer</td>
<td>51(57%)</td>
<td>1.1 (0.65-1.7)</td>
</tr>
<tr>
<td>Controls: 1,040</td>
<td>1 to &lt;10 jnt-yrs</td>
<td>1 to &lt;10 jnt-yrs</td>
</tr>
<tr>
<td>Laryngeal cancer</td>
<td>564(54%)</td>
<td>1.1 (0.65-1.7)</td>
</tr>
<tr>
<td>17 Oral: 53(9%)</td>
<td>5 (9%)</td>
<td>Ever use</td>
</tr>
<tr>
<td>Oral: 53(9%)</td>
<td>20 (10%)</td>
<td>10 to &lt;30 jnt-yrs</td>
</tr>
<tr>
<td>Laryngeal cancer</td>
<td>91 (15%)</td>
<td>0.3 (0.1-1.8)</td>
</tr>
<tr>
<td>21 Oral: 16(21.3%)</td>
<td>16(21.3%)</td>
<td>Joint-years</td>
</tr>
</tbody>
</table>
## Characteristics of cases and controls

<table>
<thead>
<tr>
<th>Cases=75, head and neck cancer</th>
<th>Controls=319</th>
<th>Prevalence of marijuana use</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st tertile</td>
<td>0.4 (0.1-2.2)</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>2nd tertile</td>
<td>1.2 (0.3-4.2)</td>
<td>2nd tertile</td>
<td>1.2 (0.3-4.2)</td>
</tr>
<tr>
<td>3rd tertile</td>
<td>1.6 (0.5-2.3)</td>
<td>3rd tertile</td>
<td>1.6 (0.5-2.3)</td>
</tr>
<tr>
<td>Joint-yrs (continuous)</td>
<td>1.04 (0.97-1.11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Prevalence of marijuana use

- **HPV-16-positive:**
  - Cases: 92 HNSCC
  - Controls: 17%
  - Smoked marijuana monthly for ≥1 y
  - HPV-16(+)
    - Cases: 23%
    - Controls: 17%
    - Never: 1.0 (referent)
    - Former: 2.3 (0.98-5.4)
  - HPV-16(−)
    - Cases: 25%
    - Controls: 17%
    - Current: 4.7 (1.3-17)

- **HPV-16-negative:**
  - Cases: 296
  - Controls: 12%
  - Ever use
    - Cases: 24 (13.8%)
    - Controls: 17 (9.7%)
    - Times/day
      - 0: 1.00
      - 1: 4.0 (0.9-17.2)
      - >1: 5.4 (0.9-33)
    - Years of use
      - 0: 1.00
      - 1: 3.9 (0.99-15.0)
      - >1: 4.9 (1.07-22.3)

- **HPV-trend:**
  - SMOKED
    - Cases: 0.007
    - Controls: 0.013
    - HPV-trend
      - Cases: 0.021
      - Controls: 0.013