HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Int J Cancer. 2020 August 01; 147(3): 866–875. doi:10.1002/ijc.32823.

Tobacco smoking, chewing habits, alcohol drinking and the risk of head and neck cancer in Nepal

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Abstract

Although tobacco smoking, pan chewing, and alcohol drinking are important risk factors for head and neck cancer (HNC), the HNC risks conferred by products available in Nepal for these habits are unknown. We assessed the associations of tobacco smoking, chewing habits, and alcohol drinking with HNC risk in Nepal. A case-control study was conducted in Nepal with 549 incident HNC cases and 601 controls. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression adjusting for potential confounders. We observed increased HNC risk for tobacco smoking (OR: 1.54; 95% CI: 1.14, 2.06), chewing habits (OR: 2.39; 95% CI: 1.77, 3.23), and alcohol drinking (OR: 1.57; 95% CI: 1.14, 2.18). The population attributable fraction (PAF) was 24.3% for tobacco smoking, 39.9% for chewing habits, and 23.0% for alcohol drinking. Tobacco smoking, chewing habits, and alcohol drinking might be responsible for 85.3% of HNC cases. Individuals who smoked tobacco, chewed products, and drank alcohol had a 13-fold increase in HNC risk (OR: 12.83; 95% CI: 6.91, 23.81) compared to individuals who did not have any of these habits. Both high frequency and long duration of these habits were strong risk factors for HNC among the Nepalese with clear dose-response trends. Preventive strategies against starting these habits and support for quitting these habits are necessary to decrease the incidence of HNC in Nepal.

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Conflict of interest

Marcus Monroe has a potential financial conflict of interest as follows: (1) Advisory Board for Sanofi-Genzyme/Regeneron for non-melanoma skin cancer. (2) NIH (NIDCR) funded research grant evaluating late effects in head and neck cancer survivors (HNC). (3) American Head and Neck Society (AHNS) grant for HNC survivor research. The other authors declare no conflicts of interest.

Keywords

alcohol; chewing; head and neck cancer; Nepal; tobacco

Introduction

Head and neck cancer (HNC), refers to a group of neoplasms originating in the oral cavity, oropharynx, hypopharynx, and larynx. There were an estimated 705,800 new HNC cases and 358,100 deaths from HNC worldwide in 2018.[1] In Nepal, the incidence and mortality rates of HNC ranked third among all cancer sites, with an estimated 2,300 new cases and 1,500 deaths.[1] The International Agency for Research on Cancer (IARC) Monographs on the evaluation of carcinogenic risks to humans concluded that tobacco smoking, tobacco chewing, betel quid (pan) chewing with and without tobacco, and alcoholic beverages are causally related to cancers of the oral cavity and pharynx in humans with sufficient evidence.[2] The use of smoke or smokeless tobacco products results in exposure to over 70 known carcinogens, such as tobacco-specific nitrosamines (TSNA), polycyclic aromatic hydrocarbons (PAH), etc.[3-6] Alcohol drinking may cause HNC through the carcinogenic effects of ethanol and acetaldehyde by disrupting DNA synthesis and repair, forming stable DNA adducts by binding to DNA, and altering the expression of oncogenes by DNA hypomethylation.[7-9] The Nepal demographic and health survey reported that the prevalence of tobacco smoking was 27% among men and 6% among women while the prevalence of smokeless tobacco use was 40% among men and 3% among women.[10] The comprehensive tobacco control law in 2011 required all tobacco products (cigarettes, bidi, and smokeless tobacco) to show pictorial health warning labels on both sides of the package, 100% smoke free public places and workplaces, a complete ban on tobacco advertising, and a ban on sales to people < 18 years old and to pregnant women.[11] According to a World Health Organization (WHO) report, the prevalence of current alcohol drinkers was 12% among men and 4% among women in Nepal.[12] The comprehensive alcohol control law in 2017 required all alcohol containers to show pictorial health warning labels, a complete ban on alcohol advertisement, a ban on sales in public places, a ban on serving alcohol in government-sponsored programs and events, and a restriction on alcohol sales for certain hours in licensed shops.[13, 14] Other potential risk factors of HNC, including involuntary smoking, poor diet, and household air pollution, are also important factors for cancer prevention in Nepal.[15-18]

Previous studies have consistently reported that the risk of HNC increases with the duration and intensity of tobacco smoking, smokeless tobacco (chewing tobacco and snuff), and alcohol drinking.[19-30] Moreover, cigarette smoking and alcohol drinking presented a greater than multiplicative interaction on HNC risk. An analysis of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cohort reported 66% of HNC cases were attributed to cigarette smoking and/or alcohol drinking .[20] In addition, Lee et at. reported that 47.2% of HNC cases in East Asia were attributed tobacco and/or alcohol using data from a multicenter-case-control study.[31] Evaluating the burden of HNC risks due to tobacco smoking, chewing habits, and alcoholic drinking is important for public health in Nepal.

Currently, there are no estimates on the associations of tobacco smoking, chewing habits, and alcoholic drinking with the risk of HNC among the Nepalese. HNC risk estimates specific to Nepal will provide policymakers and health managers with important information to support cancer prevention strategies in Nepal. Therefore, we conducted a hospital-based case-control study at the B.P. Koirala Memorial Cancer Hospital (BPKMCH), which is the National Cancer Center and the main cancer referral center in Nepal, in order to (1) estimate HNC risk for types of tobacco smoking, chewing, and alcohol drinking habits; (2) evaluate how duration and frequency of tobacco smoking, chewing habits, and alcoholic drinking are associated with HNC risk; and (3) estimate the joint effect of tobacco smoking, chewing, and alcohol drinking habits on HNC risk.

Material and Methods

Study population

A hospital-based case-control study was conducted at BPKMCH, located in the Chitwan district of Nepal. Between 2016 to 2018, we recruited HNC cases and frequency-matched controls by age (±5 years), sex, race/ethnicity, and residential area. The inclusion criteria for HNC cases were that they (1) were patients at the BPKMCH; (2) had been a resident of Nepal for at least five years; and (3) were 18 years of age or older. The sub-sites of HNC included the oral cavity, oropharynx, hypopharynx, and larynx. Cancer cases of the salivary gland (including parotid glands), nasopharynx, and thyroid were excluded. Incident cancer cases were recruited within three months after the initial diagnosis. False positive cases were excluded after the final pathological diagnosis. The inclusion criteria for the hospital-based controls were that individuals had to be: (1) cancer-free, (2) older than 18 years of age, and (3) visiting BPKMCH. The reasons for visiting the hospital included cancer screening (22.0%), hospital visitors (63.6%), or both hospital visitors and cancer screening subjects (14.5%). Cases and controls were recruited over the same time period from April 2016 to July 2018.

In-person interviews were conducted by trained staff members using the questionnaire to collect information on demographic factors, occupational history, dietary factors, medical history, residential history, reproductive history (women only), quality of life (cases only), and a detailed history of tobacco smoking, chewing habits, and alcohol consumption. Information on tobacco smoking, chewing, and alcohol drinking collected by the questionnaire included start and quit age, and frequency (quantity per day). The study was approved by the Institutional Review Boards (IRBs) at the University of Utah (IRB_00040682) and the Nepal Health Research Council. All participants provided written informed consent.

Of the 652 subjects invited to participate in the study as cases, 602 agreed to participate in the study (participation rate = 92.3%). After the final pathological diagnosis, 53 cases were excluded due to ineligible cancer sites and 549 HNC cases were included in the final analyses. Of the 643 subjects invited to participate in the study as controls, 601 agreed to participate in the study (participation rate = 93.5%). Among non-participating cases (n = 50), the main reasons for nonparticipation were “ill health” (38.0%), “the study did not make sense to the respondent” (32.0%), and “no time” (20.0%). Among non-participating controls

(n = 42), the main reasons for nonparticipation were “the study did not make sense to the respondent” (38.1%), “no time” (26.2%), and “ill health” (19.1%). Nonparticipants were older and included more women compared to participants for both cases and controls.

Exposure assessment

For tobacco consumption, tobacco smoking products included in the questionnaire were cigarettes with and without filter, bidi, choor/kankat, hooka/pipe, and hashish. If participants answered yes for the question “Have you ever smoked >100 cigarette/bidi/kankat/choor over lifetime?”, they were asked to report the detailed information of the habits, including types of smoking products, age of start and end, and quantity per day. If the frequency in quantity per day increased by ≥50% or decreased by ≥50%, they were asked to report the updated quantity per day with the start and end age of this change. For example, if the participant increased the frequency of cigarette smoking from 10 to 15 cigarettes per day, they reported the start and end age of this frequency. Conversely, if the participant decreased their cigarette smoking frequency from 15 to 10 cigarettes per day, this change would be reported. The age of starting and ending tobacco smoking were used to calculate the duration of tobacco smoking. Cumulative consumption was calculated by: duration in year* quantity per day * 365.25. If more than one smoking period or quantity per day were reported, we summed the cumulative consumption calculated from the different periods. The final frequency was calculated by using final cumulative consumption divided by the overall duration, thus the frequency would be an average frequency weighted by the years of smoking at that frequency. For example, if the subject reported smoked 10 cigarettes per day from 20 to 30 years of age and smoked 20 cigarettes per day from 35 to 45 years of age, then the final cumulative consumption in the lifetime would be 109,575 cigarettes (=10*10*365.25+20*10*365.25), the duration of cigarette smoking would be 20 years, and the overall frequency would be 15 cigarettes per day (=109,575/(20*365.25)). To combine different tobacco smoking products, we needed to calculate cigarette-equivalent for the smoking products in Nepal; however, there are no reference standards of cigarette-equivalent for these products in Nepal. For example, Gajalakshmi et al. used a weight of 0.25 whereas others used 0.5 for bidi[32, 33], and those weights were based on users in India. In our study, a cigarette-equivalent was calculated for bidi and choor/kankat by assigning a weight of 1 (1 cigarette = 1 bidi = 1 choor/kankat). Hooka/pipe and hashish were not included in the total tobacco estimate because the frequency of consumption on those products was very low and we decided to analyze these separately. Thus, smokers for tobacco smoking were defined as subjects who formerly or currently used cigarettes (with and without filter), bidi, choor/kankat, and vice versa for non-smokers.

Similar to tobacco smoking, participants who ever consumed chewing products were asked to report types of chewing habits (yes/no), start and end age, and quantity per day. Several chewing products were included in the questionnaire: pan (with and without tobacco), pan masala (with and without tobacco), khaini, surti, zarda, zarda and kiwam, supari, and lwang. If the quantity of the chewing habit changed more than 50%, the updated quantity and age range were reported. The cumulative consumption of chewing habits was calculated as the product of the number of chewing product per day and the duration of this habit. Chewers

were defined as subjects who ever consumed (formerly or currently) any type of chewing products, and vice versa for non-chewers.

Regarding alcohol consumption, participants were asked to report on the types of alcoholic beverages, start and end age, days per week of that alcoholic beverage type, and units per day. “units per day” represented how many milliliters (ml) or liters of the alcohol beverage consumed per day. We transferred the unit to ml (1 liter = 1000 ml). Alcoholic beverages included beer, whisky, rakshi, jaand/chayang, thongha, and wine. About 40% of controls drank rakshi, which is a traditional distilled alcoholic beverage in Nepal, India, and Tibet. The percentage of ethanol was 25% for rakshi, 12% for jaand/chayang, and 5.5% for thongba.[34, 35] We defined one drink as 15.6 ml of pure ethanol based on an international average calculated by the International Head and Neck Cancer Epidemiology Consortium.[36] We calculated amounts of pure ethanol intake for alcohol consumption. The cumulative ethanol consumption (ml) was calculated by: duration * days per week * units per day * 52 * weight for the type of drink. The frequency (drinks/day) was calculated by using cumulative ethanol consumption divided by the product of overall duration and 15.6 ml.[36] Drinkers for alcohol drinking were defined as subjects who ever consumed (formerly or currently) any type of alcohol drinking, and vice versa for non-drinkers.

Statistical analysis

Chi-square tests were used to compare the distribution of demographic characteristics between cases and controls. Unconditional logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (95% CI). The following covariates were included in the models to adjust for potential confounders: age (continuous), sex, education levels (categories shown in Table 1), race/ethnicity (categories shown in Table 1), family monthly income (categories shown in Table 1), residential area (categories shown in Table 1), and the duration and frequency of tobacco smoking, chewing, and alcohol drinking (continuous), interaction among frequency of tobacco smoking, chewing habits, and alcohol drinking (continuous), where appropriate. P for trend was estimated for a dose-response association by testing the linear trend between HNC risk and the levels of exposure of interest.[37] We used variance inflation factor (VIF) to examine multicollinearity among the independent variables.[38] The population attributable fractions (PAFs) were estimated for tobacco smoking, chewing habits, and alcohol drinking based on the Miettinen formula PAF=p(ec) * (1 – 1/OR), where p(ec) is the proportion of exposure among cases.[24, 39, 40] ORs adjusted for potential confounding factors were used in the equations. The PAF is an estimated fraction of all HNC cases that would not have occurred if there had been no exposure.[41] When we estimated the association of HNC risk for type of smoking, one group included all subjects with adjustment of chewing habits and alcohol drinking (duration, frequency, and interaction) and another group excluded ever-chewers and ever-drinkers. The same method was used for types of chewing habits and alcohol drinking. When estimating the associations of HNC risk for tobacco smoking, chewing habits, or alcohol drinking, we adjusted for the two other habits. For example, when tobacco smoking was the exposure of interest, we adjusted for age, sex, education levels, race/ethnicity, family monthly income, residential area, duration and frequency of chewing habits and alcohol drinking, and the interaction term between chewing habits and alcohol drinking (frequency).To estimate the

possible effect modification among the three habits of tobacco smoking, chewing habits, alcohol drinking, and HNC risk, we categorized the exposure to 8 levels, from non-smokers, non-chewers, and non-drinkers to ever-smokers, ever-chewers, and ever-drinkers. The reference group was non-smokers, non-chewers, and non-drinkers. Interactions on an additive scale were estimated using the Relative Excess Risk due to Interaction (RERI).[42, 43] If there were 2 dichotomous factors, A and B, and we let OR_{ij} denote the OR comparing A = i and B = j with A = B = 0, then the RERI for the OR is defined by $OR_{11} - RR_{10} - RR_{01} + 1$.[44] No interaction is suggested on the additive scale when the combined effect of two exposures is equal to the sum of the individual effects of the two exposures (RERI = 0). A super-additive interaction is supported when RERI > 0 and the sub-additive interaction is supported when RERI < 0. Interactions on a multiplicative scale were estimated using the ratio of odds ratios (ROR). ROR is defined by $OR_{11}/OR_{01}*OR_{10}$. No interaction is suggested on a multiplicative scale when the combined effect is equal to the product of the individual effects of the two exposures (ROR = 1). A super-multiplicative interaction is supported when ROR > 1, and a sub-multiplicative interaction is supported when ROR < 1. Sensitivity analyses were conducted by including more variables in the statistical model to ensure the associations were robust. The variables we used included: second hand smoking (yes/no), diet (frequency per week of red meat, fish, and vegetable consumption, continuous), household air pollution (low/ medium/heavy). All analyses were performed using the SAS system, version 9.4 (SAS Institute, Cary, NC). All P-values were two-sided.

Data Availability

The data that support the findings of this study are available upon request with appropriate approvals including IRB approval.

Results

Of 549 HNC cases and 601 controls, the controls were more educated and earned higher incomes than the HNC cases (Table 1). The matching factors (age, sex, race/ethnicity, and residential area) were distributed evenly among HNC cases and controls.

For the type of tobacco smoking, more than 20% of controls smoked cigarettes (32.1% for filter cigarettes and 20.3% for non-filter cigarettes), and approximately 19% and 10% of controls smoked bidi and choor/kankat, respectively (Table 2). Individuals who had ever smoked filter cigarettes had 1.42 times risk of HNC (95% CI: 1.06, 1.90) compared with those who had not smoked filter cigarettes. Interestingly, the association with HNC risk appeared to be stronger among filter cigarette smokers than non-filter cigarette smokers (OR for non-filter cigarette: 1.31; 95% CI: 0.93, 1.86). When we excluded ever-chewers and ever-drinkers in the analysis to estimate the association for the subjects with a single habit, the 95% CIs became wider due to the smaller sample size (Supplemental Table 1). Among all types of chewing habits, surti was the most frequently used by the Nepalese study population (35.3% of controls and 47.7% of cases were ever users). Chewing habits of surti and zarda were associated with elevated HNC risk (OR for surti: 1.75, 95% CI: 1.31, 2.33; OR for zarda: 3.02, 95% CI: 1.87, 4.88). Surti is a chewing product containing dried tobacco leaves,[45] and zarda is another chewing product containing tobacco leaves, limes, areca nut,

spices, and tannins.[46] For the type of chewing without tobacco, we observed an increased risk of HNC for chewing supari, which is areca nut (betel nut) (OR: 3.50, 95% CI: 1.85, 6.59). After excluding ever-smokers and ever-drinkers in the analyses, the conclusion did not change even though some of the point estimates became higher (Supplemental Table 1). For types of alcohol drinking, we did not observe the association between any type of alcoholic beverage and HNC risk, but overall alcohol drinking was positively associated with HNC risk (shown in Table 3). We did not show the type of habits if less than 3% of controls had it.

After adjusting for chewing habits and alcohol drinking, tobacco smoking had a 1.54 fold increased risk of developing HNC compared with those who did not smoke tobacco (95% CI: 1.14, 2.06; PAF: 24.3%; Table 3). Moreover, the monotonic associations were shown for frequency and duration of tobacco smoking (p for trend < 0.001). Consuming chewing products was associated with a 2.39 fold increase in risk of developing HNC compared with those who did not have chewing habits (95% CI: 1.77, 3.23; PAF: 39.9%; Table 3). Similar to tobacco smoking, higher frequency and duration of chewing habits were monotonically associated with HNC risk (p for trend < 0.001) after adjusting for the duration and frequency of tobacco smoking and alcohol drinking. Individuals who had consumed alcoholic beverages had a 1.57 times risk of HNC compared with those who did not drink alcoholic beverages (95% CI: 1.14, 2.18; PAF: 23.0%; Table 3) after adjusting for tobacco smoking and chewing habits. HNC risk was positively associated with higher frequency and duration of alcohol drinking. The results were essentially the same when we adjusted for second hand smoking, diet, and household air pollution in the models (Supplemental Table 2).

Individuals who had all three habits of tobacco smoking, chewing habits, and alcohol drinking had a HNC risk of 12.83 compared to individuals who did not have any of those habits (95% CI: 6.91, 23.81; PAF: 29.1%; Table 4). Only 4.2% of cases did not have any of those habits compared with 20% of controls. Among the three exposures of interest, the chewing habit alone was associated with the largest OR of 11.64, although the 95% confidence interval was quite wide (95% CI: 6.13, 22.09). Among non-chewers, there was a more than additive interaction between tobacco smokers and alcohol drinkers (Supplemental Table 3). However, among chewers, the interaction between tobacco smokers and alcohol drinkers was more than multiplicative (ROR: 2.11, 95% CI: 1.04, 4.27). When we adjusted for fewer covariates (age, sex, and race/ethnicity), the ORs were similar to the full model shown in Table 4 (Supplemental Table 4). VIF for the independent variables was less than 5 in all models (Supplemental Table 5-7).

Discussion

In this study, we observed that increasing duration and frequency of tobacco smoking, chewing habits, and alcohol drinking increases HNC risk with clear dose-response trends in a Nepalese population. Individuals who had all three habits of tobacco smoking, chewing habits, and alcohol drinking had a 12.83 times (95% CI: 6.91, 23.81) greater risk of developing HNC compared with individuals without these habits. Among Nepalese people, cigarette with filter and chewing products—namely, surti, zarda, and supari—were associated with increased HNC risk.

Our results are consistent with previous studies that tobacco smoking, chewing habits, and alcohol drinking are associated with increased HNC risk.[23, 31, 47-49] Pooled analyses using data from the International Head and Neck Cancer Epidemiology Consortium (INHANCE) supported the association between low-frequency tobacco smoking and increased HNC risk.[48] We also observed that people who smoked <10 cigarettes per day had a higher risk of developing HNC (OR, 1.40; 95% CI: 1.02, 1.91). We included chewing products without tobacco, such as pan, pan masala, supari, and lwang, in the analyses. Moreover, our results suggested an elevated risk of developing HNC for chewing supari, which is composed of areca (betel) nut that contains carcinogenic compounds arecoline and nitrosoamine.[46] We observed an increased risk of HNC for high frequency and duration of overall alcohol drinking, but not for the individual type of drinking products. Our study had limited statistical power to assess the associations of alcoholic beverages with HNC risk. The highest statistical power among types of alcohol drinking was 60% for rakshi. The low statistical power may be one of the reasons why we were unable to detect a moderate association between those products and HNC risk. However, the statistical power was larger than 90% when we combined types of alcohol drinking.

In terms of duration of habits and the risks conferred, pooled analyses including 19,600 HNC cases and 25,566 controls reported that for individuals who smoked >0–3 cigarettes per day, the risk of HNC increased significantly after 30 years of smoking compared with non-smokers (OR: 2.64, 95% CI: 1.92, 3.63). For individuals who smoked > 3 cigarettes per day, the HNC risk was higher after 20 years of consumption.[48] For alcohol drinking, another pooled analyses including 9,107 HNC cases and 14,219 controls reported an increased HNC risk after 20 years of beer, liquor, or wine consumption compared with non-drinkers.[36] Our results are consistent with previous studies that an increased HNC risk was observed for > 25 years of tobacco smoking and > 20 years of alcohol drinking.[31, 36, 48]

Previous meta-analyses of 12 epidemiologic studies reported an increased risk of oral cavity cancer for bidi smokers (OR: 3.1, 95% CI: 2.0, 5.0).[50] Our study observed the same association after excluding ever-drinkers and ever-smokers. Several studies confirmed the combined effect of tobacco smoking and alcohol drinking on the risk of head and neck cancer, [23, 24, 49, 51, 52] but only a few studies estimated the interaction among three habits including tobacco smoking, chewing habits, and alcohol drinking on HNC risk.[31, 32] A case-control study conducted among Indian men reported increased oral cavity, pharyngeal, and esophageal cancer risks for tobacco smoking, tobacco chewing, and alcohol drinking (OR for oral cancer:16.34; 95% CI: 12.13, 22.00).[32] A multicenter case-control study in East Asia reported an OR of 20.60 (95% CI: 11.75, 36.12) on HNC risk for the joint exposure of tobacco smoking, betel quid chewing, and alcohol drinking.[31] In our study, the strength of the association was smaller (OR, 12.83; 95% CI: 6.91, 23.81) possibly because we included not only betel quid chewing or tobacco chewing, but also several types of chewing products with or without tobacco. The PAFs for tobacco smoking were similar between our study and the East Asia study (24.3% in Nepal vs. 24% in East Asia). However, the PAF for chewing habits was higher in our study (39.9% in Nepal vs. 28.7% in East Asia) due to the high prevalence of chewing habits in Nepal. Our results show that the OR for individuals with chewing habits only was higher than OR for individuals with tobacco smoking and chewing habits or individuals with chewing habits and alcohol drinking but the CIs were overlapped.

Overlapped CIs of the ORs were also observed in a previous study conducted in East Asia with 921 HNC cases and 806 controls.[31]

Pooled analyses using data from the INHANCE reported a greater than multiplicative joint effect between tobacco smoking and alcohol drinking, with an OR of 5.73 (95% CI: 3.62, 9.06).[24] We observed a greater than multiplicative interaction between tobacco smoking and alcohol drinking among ever-chewers after adjusting for the duration and frequency of chewing habits. For non-chewers, we observed a greater than additive interaction between tobacco smoking and alcohol drinking. This difference could be attributed to the correlation among tobacco smoking, chewing habits, and alcohol drinking. That is, residual confounding may be present when we adjusted for chewing habits among ever-chewers.

A cross-sectional study in Nepal involving 1,540 adolescent students reported that 66% of non-tobacco users had good knowledge that tobacco could harm their health, but only 31% of tobacco users had good knowledge of this information.[24] Since 2015, warning labels highlighting harmful effects of tobacco have been legally required to cover 90% of tobacco (smoking and chewing products) packaging in Nepal.[53] The warning labels may inform tobacco users that tobacco is harmful. Our study shows that supari, a chewing product without tobacco, could also increase the risk of HNC. That is, even without tobacco, chewing supari was associated with a 3.5 fold increase of HNC risk, highlighting the need for preventive strategies against chewing products without tobacco.

A limitation in our study is that recall bias may have influenced the results if cases recalled more details of their tobacco smoking, chewing habits, and alcohol drinking history. Our study was unable to adjust for human papillomavirus (HPV) infection, which is an effect-measure modifier of the smoking effect on HNC among ever-tobacco-users.[54] HPV infection is primarily linked with oropharyngeal cancer.[55] Therefore, we further examined the association without including oropharyngeal cancer cases, and the inferences remained consistent. Thus, HPV infection may not be a strong confounder in our study. Due to the limited sample size, we were not able to estimate the association by different cancer sub-sites such as oral cavity or laryngeal cancer. Also, the 95% confident intervals were wide when we examined the joint effects of tobacco smoking, chewing habits, and alcohol drinking because only 23 cases did not have a history of tobacco smoking, chewing habits, or alcohol drinking. Lastly, biomarkers for tobacco smoking were not collected and our estimates were based on self-reported history. However, in the questionnaire, we were able to collect lifetime tobacco exposure and we took into account the change of tobacco consumption in different time periods instead of just a one-time point from the biomarkers.

The major strength of this study is that we collected detailed exposure history of tobacco smoking, chewing habits, and alcohol drinking, which allowed for HNC risk estimates with adjustment for potential confounders and took into account changes in individuals' behaviors over their lifetime. We collected frequently used products in Nepal, including six types of smoking tobacco products, ten types of chewing products, and six types of alcoholic beverages. To our knowledge, our study is the first to estimate how tobacco smoking, chewing habits, and alcohol drinking are associated with HNC risk in Nepal.

In conclusion, the results of this study support a strong association and burden of tobacco smoking, chewing habits, and alcohol drinking on HNC risk in Nepal. These habits were individually and jointly associated with the risk of HNC. Individuals who smoked cigarettes with filters, chewed surti, zarda, or supari have higher risks of developing HNC. Preventive strategies against these products are necessary to decrease the incidence of HNC in Nepal, such as cessation programs for tobacco smoking, chewing habits, and alcohol drinking, raising the taxation on tobacco and alcohol, or penalties for violating tobacco and alcohol control laws to enhance implementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by a grant from the NIH 3P30 CA042014-26S6.

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WHAT'S NEW

In this case-control study in Nepal, we observed increased head and neck cancer (HNC) risks for tobacco smoking (OR: 1.54; 95% CI: 1.14, 2.06), chewing habits (OR: 2.39; 95% CI: 1.77, 3.23), and alcohol drinking (OR: 1.57; 95% CI: 1.14, 2.18). Individuals who smoked tobacco, chewed products, and drank alcohol had a 13-fold increase in HNC risk (OR: 12.83; 95% CI: 6.91, 23.81) compared to individuals who did not have any of these habits in Nepal.

Table 1.

Demographic characteristics of head and neck cancer cases and controls in Nepal

	Cases, n(%)	Controls, n(%)	p-value[1]
Total	549 (100)	601(100)	
Age			0.5582
<40	45 (8.2)	60 (10.0)	
40 to 49	128 (23.3)	146 (24.3)	
50 to 59	187 (34.1)	213 (35.4)	
60 to 69	151 (27.5)	142 (23.6)	
≥70	38 (6.9)	40 (6.7)	
Sex			0.9728
Male	438 (79.8)	479 (79.7)	
Female	111 (20.2)	122 (20.3)	
Ethnicity			0.3915
Brahmin	70 (12.8)	107 (17.8)	
Chettri	99 (18.0)	106 (17.6)	
Rai	24 (4.4)	22 (3.7)	
Madishe	173 (31.5)	169 (28.1)	
Limbu	10 (1.8)	14 (2.3)	
Magar	50 (9.1)	54 (9.0)	
Tharu	38 (6.9)	34 (5.7)	
Other	85 (15.5)	95 (15.8)	
Education			<0.0001
None	269 (49.0)	192 (31.9)	
≤ 3rd grade	65 (11.8)	65 (10.8)	
4th-7th grade	93 (16.9)	103 (17.1)	
High school	108 (19.7)	177 (29.5)	
> High school	14 (2.6)	64 (10.6)	
Family monthly income (Rupees)			<0.0001
<500	13 (2.4)	2 (0.3)	
500 to 999	42 (7.7)	27 (4.5)	
1000 to 1999	112 (20.4)	78 (13.0)	
2000 to 4999	155 (28.2)	134 (22.3)	
≥ 5000	227 (41.3)	360 (59.9)	
Residential area			0.8687
Plain	387 (70.5)	432 (71.9)	
Hill	150 (27.3)	157 (26.1)	
Mountain	12 (2.2)	12 (2.0)	

[1] p-value for chi-square test

Table 2.

Types of tobacco smoking, chewing habits, alcohol drinking, and the risk of head and neck cancer in Nepal

		Cases, n(%)	Controls, n(%)	OR (95% CI)[1]	P-value[1]
Type of smoking[2]					
Cigarette with Filter					
	No	331 (60.3)	408 (67.9)	Reference	
	Yes	218 (39.7)	193 (32.1)	1.42 (1.06, 1.90)	0.0200
Cigarette without Filter					
	No	382 (69.6)	479 (79.7)	Reference	
	Yes	167 (30.4)	122 (20.3)	1.31 (0.93, 1.86)	0.1249
Bidi					
	No	377 (68.7)	489 (81.4)	Reference	
	Yes	172 (31.3)	112 (18.6)	1.25 (0.90, 1.75)	0.1868
Choor/Kankat					
	No	482 (87.8)	543 (90.3)	Reference	
	Yes	67 (12.2)	58 (9.7)	0.68 (0.43, 1.09)	0.1097
Type of chewing[3]					
Pan					
	No	505 (92.0)	558 (92.8)	Reference	
	Yes	44 (8.0)	43 (7.2)	0.93 (0.55, 1.58)	0.7949
Khaini					
	No	454 (82.7)	509 (84.7)	Reference	
	Yes	95 (17.3)	92 (15.3)	1.03 (0.70, 1.50)	0.8967
Surti					
	No	287 (52.3)	389 (64.7)	Reference	
	Yes	262 (47.7)	212 (35.3)	1.75 (1.31, 2.33)	0.0002
Zarda					
	No	479 (87.2)	564 (93.8)	Reference	
	Yes	70 (12.8)	37 (6.2)	3.02 (1.87, 4.88)	<0.0001
Pan masala					
	No	522 (95.1)	579 (96.3)	Reference	
	Yes	27 (4.9)	21 (3.5)	1.76 (0.90, 3.41)	0.0973
Supari (without tobacco)					
	No	512 (93.3)	582 (96.8)	Reference	
	Yes	37 (6.7)	19 (3.2)	3.50 (1.85, 6.59)	0.0001
Type of drinking[4]					
Beer					
	No	488 (88.9)	523 (87.0)	Reference	
	Yes	61 (11.1)	78 (13.0)	0.96 (0.61, 1.53)	0.8751
Whisky					
	No	479 (87.2)	525 (87.4)	Reference	

		Cases, n(%)	Controls, n(%)	OR (95% CI)[1]	P-value[1]
	Yes	70 (12.8)	76 (12.6)	1.24 (0.81, 1.92)	0.3259
Rakshi					
	No	238 (43.4)	350 (58.2)	Reference	
	Yes	311 (56.6)	251 (41.8)	1.29 (0.93, 1.78)	0.1293
Jaand/Chayang					
	No	408 (74.3)	512 (85.2)	Reference	
	Yes	141 (25.7)	89 (14.8)	1.46 (0.96, 2.24)	0.0794
Thongba					
	No	524 (95.4)	581 (96.7)	Reference	
	Yes	25 (4.6)	20 (3.3)	1.05 (0.45, 2.44)	0.9035

Abbreviations: CI, confidence interval; OR, odds ratio

[1]Adjusted for age, sex, education levels, race/ethnicity, family monthly income, residential area, tobacco smoking (duration and frequency), chewing habits (duration and frequency), alcohol drinking (duration and frequency), and the interaction between tobacco smoking, chewing habits, and alcohol drinking (frequency), when appropriate.

[2]Additionally adjusted for duration and frequency of cigarette, bidi, choor/kankat, hooka/pipe, hashish, when appropriate.

[3]Additionally adjusted for duration and frequency of surti, zarda, and supari, when appropriate.

[4]Additionally adjusted for duration and frequency of beer, whisky, rakshi, jaand/chayang, thongba, when appropriate.

Table 3.

Frequency and duration of tobacco smoking, chewing habits, alcohol drinking on the risk of head and neck cancer for in Nepal

	Cases, n(%)	Controls, n(%)	OR (95% CI)[1]	P-value[1]	PAF
Tobacco smoking[2]					
Ever consumed					
No	169 (30.8)	286 (47.6)	Reference		
Yes	380 (69.2)	315 (52.4)	1.54 (1.14, 2.06)	0.0043	24.3%
Frequency (cigarettes-equivalent/day)[5]					
0	169 (30.8)	286 (47.6)	Reference		
> 0 to 10	206 (37.5)	202 (33.6)	1.40 (1.02, 1.91)	0.0368	10.7%
> 10	174 (31.7)	112 (18.6)	2.01 (1.36, 2.97)	0.0005	15.9%
Duration (years)[5]					
0	169 (30.8)	286 (47.6)	Reference		
> 0 to 25	114 (20.8)	152 (25.3)	1.12 (0.79, 1.59)	0.5092	2.2%
> 25	266 (48.5)	162 (27.0)	2.20 (1.54, 3.14)	<0.0001	26.4%
Chewing habits[3]					
Ever consumed					
No	172 (31.3)	284 (47.3)	Reference		
Yes	377 (68.7)	317 (52.7)	2.39 (1.77, 3.23)	<0.0001	39.9%
Frequency (numbers/day)[5]					
0	172 (31.3)	284 (47.3)	Reference		
> 0 to 6	156 (28.4)	159 (26.5)	1.95 (1.37, 2.76)	0.0002	14.0%
> 6	215 (39.2)	153 (25.5)	2.91 (2.06, 4.12)	<0.0001	26.0%
Duration (years)[5]					
0	172 (31.3)	284 (47.3)	Reference		
> 0 to 20	136 (24.8)	145 (24.1)	1.86 (1.29, 2.67)	0.0008	11.6%
> 20	236 (43.0)	167 (27.8)	2.92 (2.08, 4.11)	<0.0001	28.5%
Alcohol drinking[4]					
Ever consumed					
No	201 (36.6)	295 (49.1)	Reference		
Yes	348 (63.4)	306 (50.9)	1.57 (1.14, 2.18)	0.0065	23.0%
Frequency (drinks/day)[5]					
0	201 (36.6)	295 (49.1)	Reference		
> 0 to 6	103 (18.8)	149 (24.8)	1.14 (0.78, 1.65)	0.5023	2.3%
> 6	242 (44.1)	153 (25.5)	2.32 (1.57, 3.43)	<0.0001	25.2%
Duration (years)[5]					
0	201 (36.6)	295 (49.1)	Reference		
> 0 to 20	91 (16.6)	133 (22.1)	1.16 (0.78, 1.73)	0.4724	2.3%

	Cases, n(%)	Controls, n(%)	OR (95% CI)[1]	P-value[1]	PAF
> 20	257 (46.8)	171 (28.5)	2.03 (1.39, 2.94)	0.0002	23.8%

Abbreviations: CI, confidence interval; OR, odds ratio; PAF, population attributable fraction.

[1]Adjusted for age, sex, education levels, race/ethnicity, family monthly income, residential area.

[2]Additionally adjusted for chewing habits (duration and frequency), alcohol drinking (duration and frequency), and the interaction between chewing habits and alcohol drinking (frequency).

[3]Additionally adjusted for tobacco smoking (duration and frequency), alcohol drinking (duration and frequency), and the interaction between tobacco smoking and alcohol drinking (frequency).

[4]Additionally adjusted for tobacco smoking (duration and frequency), chewing habits (duration and frequency), and the interaction between tobacco smoking and chewing habits (frequency).

[5]P for trend < 0.001

Table 4.

Joint effects of tobacco smoking, chewing habits, alcohol drinking for head and neck cancer in Nepal

Tobacco smoking	Chewing habits	Alcohol drinking	Cases, n(%)	Controls, n(%)	OR (95% CI)[1]	P-value[1]	PAF
No	No	No	23 (4.2)	120 (20.0)	Reference		
No	No	Yes	8 (1.5)	43 (7.2)	2.28 (0.87, 5.95)	0.0931	0.8%
Yes	No	No	36 (6.6)	58 (9.7)	2.78 (1.45, 5.34)	0.0021	4.2%
No	Yes	No	76 (13.8)	54 (9.0)	11.64 (6.13, 22.09)	<0.0001	12.7%
Yes	Yes	No	66 (12.0)	63 (10.5)	8.29 (4.33, 15.89)	<0.0001	10.6%
No	Yes	Yes	62 (11.3)	69 (11.5)	9.02 (4.66, 17.43)	<0.0001	10.0%
Yes	No	Yes	105 (19.1)	63 (10.5)	15.38 (7.90, 29.94)	<0.0001	17.9%
Yes	Yes	Yes	173 (31.5)	131 (21.8)	12.83 (6.91, 23.81)	<0.0001	29.1%

Abbreviations: CI, confidence interval; OR, odds ratio; PAF, population attributable fraction.

Total PAF: 85.3%; P for trend < 0.0001

[1]Adjusted for age, sex, race/ethnicity, education levels, family monthly income, residential area.