Hookah smoking, nass chewing, and oesophageal squamous cell carcinoma in Kashmir, India

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BACKGROUND: Although cigarette smoking is an established risk factor for oesophageal squamous cell carcinoma (ESCC), there is little information about the association between other smoking and smokeless tobacco products, including hookah and nass, and ESCC risk. We conducted a case–control study in Kashmir Valley, India, where hookah smoking, nass chewing, and ESCC are common, to investigate the association of hookah smoking, nass use, and several other habits with ESCC.

METHODS: We recruited 702 histologically confirmed ESCC cases and 1663 hospital-based controls, individually matched to the cases for age, sex, and district of residence from September 2008 to January 2012. Conditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs).

RESULTS: Ever-hookah smoking (OR = 1.85; 95% CI, 1.41–2.44) and nass chewing (OR = 2.88; 95% CI, 2.06–4.04) were associated with ESCC risk. These associations were consistent across different measures of use, including intensity, duration, and cumulative amount of use, and after excluding ever users of the other product and cigarette smokers. Our results also suggest an increased risk of ESCC associated with ever-gutka chewing and -bidi smoking. However, the latter associations were based on small number of participants.

CONCLUSION: This study shows that hookah and nass use are associated with ESCC risk. As prevalence of hookah use seems to be increasing among young people worldwide, these results may have relevance not only for the regions in which hookah use has been a traditional habit, but also for other regions, including western countries.

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men and women, respectively, in the 1980s (Khuroo et al, 1992). Oesophageal cancer constitutes more than 20% of all cancers (Mattoo and Kaul, 1974; Dhar et al, 1993), and ESCC is the most common type of oesophageal cancer in the region (Malik et al, 2011). Although a few earlier studies have pointed to potential associations between some lifestyle, dietary and genetic factors, and ESCC in the Kashmir Valley (Maqbool and Ahad, 1976; Khan et al, 2011; Malik et al, 2011), little is established about the risk factors of ESCC in the region. Relatively high prevalence of hookah smoking and nass chewing (Siddiqi and Preussmann, 1989; Mir and Dar, 2009) suggests that these habits may be among the important risk factors for ESCC in the valley.

To investigate risk factors of ESCC in the Kashmir Valley, we conducted a case-control study in the region, and collected detailed information on multiple lifestyle factors. In this article, we report the association between several habits, including hookah smoking, gutka (also known as gutkha and chutka, a mixture of tobacco, areca nut, lime, and several other substances, such as flavourings and sweeteners; Javed et al, 2010) and nass chewing, and cigarette and bidi (temburni leaf and tobacco; IARC Working Group, 2004) smoking, and ESCC risk. Any association between tobacco use and ESCC in this population is unlikely to be biased by a confounding effect of alcohol, a major risk factor of ESCC in western populations (IARC Working Group, 2012), as alcohol drinking is negligible in Kashmir Valley (Mir and Dar, 2009).

**METHODS**

**Case and control selection**

This study was conducted from September 2008 to January 2012. All cancer cases were recruited at the Regional Cancer Centre and Department of Radiation Oncology of Sher-i-Kashmir Institute of Medical Sciences (SKIMS), located in Srinagar, the largest and central city in Kashmir Valley. SKIMS is the only tertiary care hospital in the whole Kashmir Valley, and all patients with cancer and some patients with other diseases are referred to from Srinagar and from 10 hospitals in the surrounding districts. All newly diagnosed cases of oesophageal cancer with histopathologically confirmed ESCC, who were above the age of 18 years and did not have any previous cancer, were invited to participate in this study.

For each case subject, we attempted to recruit at least one hospital-based control, individually matched to the case for sex, age (±5 years), and district of residence. For all cases from Srinagar and 30% of cases from other areas, we were able to recruit controls from the patients that resided in the same districts as the cases from in-patient wards of SKIMS and the Government Medical College Hospital, Srinagar. For the remaining cases (i.e., 70% of cases from areas other than Srinagar), controls were enrolled from in-patient wards of the district hospitals in the districts from where their respective cases were referred. Therefore, matching for district of residence was complete. The major reasons for hospitalisations of the enroled controls are listed in Supplementary Table 1. The maximum interval between recruitment of cases and controls was 6 months. The participation rate for cases and control was 96% (732 invited, 30 refusals) and 98% (1697 invited, 34 refusals), respectively. The majority of those who refused were too ill to participate in the study. This study was reviewed and approved by the Institutional Ethics Committee of SKIMS.

**Data collection**

Structured questionnaires were administered in face-to-face interviews by trained interviewers at hospitals. Data on socio-demographic factors, including age, sex, ethnicity, religion, place of residence, and education and lifestyle factors were collected.

Detailed information on life-long history of use, with starting and stopping ages, and daily amount of use, was obtained for several tobacco products and cannabis. Any change in the type of tobacco products and amount of use was also recorded. Ever use of gutka, nass, hookah, cigarette, bidi, and cannabis was defined as the use of the respective product at least weekly for a period of 6 months or more. For chewing tobacco products, the usual site of placement of nass/gutka in the mouth, and for hookah smoking, the usual frequency of changing water in the hookah apparatus was recorded. In hookah smoking, the smoke from charcoal-heated tobacco passes through a water basin before inhalation (Maziak, 2011). Therefore, some harmful constituents of tobacco may accumulate in the water with every session of smoking. Information on ever-alcohol use (alcohol drinking at least weekly for 6 months or more) was also collected. To minimise the inter-individual variation, a limited number of staff conducted the interviews and no proxies were used.

**Statistical analysis**

Numbers and percentages by case status were calculated and presented for categorical variables. Only small numbers of participants had used gutka, bidi, and alcohol; therefore, data for these variables are presented as ever- vs never-use only. Results for cannabis use are not shown, as only two ESCC cases and one control reported ever use of cannabis. For cigarette and hookah smoking, and nass chewing, data on intensity, duration, and cumulative amount (average intensity multiplied by duration) of use are also presented. In these variables, the never users were considered as the reference category; we attempted to classify ever users in three groups with equal number of controls in each group.

Conditional logistic regression models were used to calculate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs). The adjusted risk estimates were obtained from multivariate models in which age, ethnicity, religion, place of residence (rural/urban), education level, daily fruit and fresh vegetable intake, ever use of bidi, cannabis, gutka and alcohol, and cumulative use of cigarette, hookah, and nass were included. Fruit and vegetable intake data (grams per day) were transformed to logarithmic values following addition of 0.1 to the original values. The ORs (95% CIs) for intensity and duration of nass, hookah, and cigarette use were not adjusted for cumulative use of the respective tobacco product. By design, case and control subjects were matched by age, sex, and place of residence. Age was included in the multivariate models, because the matching for age was not perfect (±5 years). Adjustments were done for place of residence and education level as indicators of socioeconomic status and religion, because earlier studies in this region suggested dissimilar incidence of ESCC among people with different religions (Maqbool and Ahad, 1976).

We also estimated population-attributable fraction for several tobacco products in relation to ESCC using adjusted ORs and the following formula: \[ \frac{P_e (OR - 1)}{1 + P_o (OR - 1)} \] where \( P_e \) was the proportion of exposed controls (Coughlin et al, 1994). All statistical analysis were done using Stata software, version 11 (StataCorp., College Station, TX, USA). Two-sided \( P \)-values < 0.05 were considered as statistically significant.

**RESULTS**

A total of 702 ESCC cases and 1663 controls were enroled in this study. All cases had at least one matched control. Table 1 shows the distribution of demographic variables in case and control subjects. The majority of study participants were older than 50 years. Among both cases and controls, approximately 55% were male and 97% were of Kashmiri ethnic group. More ESCC cases than controls resided in rural areas (\( P < 0.001 \)). Formal education
Table 1: Demographic characteristics of ESCC cases and matched controls

| Characteristics          | ESCC cases, N (%) | Matched controls, N (%) | P-value |
|-------------------------|-------------------|-------------------------|---------|
| Total                   | 702 (100)         | 1663 (100)              | 0.002   |
| Age group, years        |                   |                         |         |
| <40                     | 19 (2.7)          | 54 (3.2)                |         |
| 40–49                   | 53 (7.5)          | 197 (11.9)              |         |
| 50–59                   | 157 (22.4)        | 424 (25.5)              |         |
| 60–69                   | 264 (37.6)        | 568 (34.2)              |         |
| ≥70                     | 209 (29.8)        | 420 (25.2)              |         |
| Mean age (i.d.), years  | 61.6 (11.1)       | 59.8 (11.1)             | <0.001  |
| Sex                     |                   |                         | 0.80    |
| Men                     | 392 (55.8)        | 919 (55.3)              |         |
| Women                   | 310 (44.2)        | 744 (44.7)              |         |
| Ethnicity               |                   |                         | 0.58    |
| Kashmiri                | 681 (97.0)        | 1618 (97.3)             |         |
| Gogri                   | 11 (1.6)          | 16 (1.0)                |         |
| Pathi                   | 9 (1.3)           | 27 (1.6)                |         |
| Other                   | 1 (0.1)           | 2 (0.1)                 |         |
| Religion                |                   |                         | 0.03    |
| Muslim                  | 694 (98.9)        | 1647 (99.0)             |         |
| Hindu                   | 5 (0.7)           | 2 (0.1)                 |         |
| Sikh                    | 3 (0.4)           | 14 (0.8)                |         |
| Place of residence      |                   |                         | <0.001  |
| Rural                   | 674 (96.0)        | 1516 (91.2)             |         |
| Urban                   | 28 (4.0)          | 147 (8.8)               |         |
| Education               |                   |                         | <0.001  |
| No formal school        | 625 (89.0)        | 1074 (64.6)             |         |
| 1–4 grade               | 33 (4.7)          | 202 (12.1)              |         |
| 5–8 grade               | 24 (3.4)          | 123 (7.4)               |         |
| High school             | 16 (2.3)          | 149 (9.0)               |         |
| College graduation      | 4 (0.6)           | 95 (5.7)                |         |
| Post-graduation         | 0 (0.0)           | 20 (1.2)                |         |
| Fruit and vegetable intake, median grams per day (interquartile range) | 1.3 (0.8–2.0) | 6.1 (2.1–72.1) | <0.001 |

Abbreviation: ESCC = oesophageal squamous cell carcinoma. Although cases and controls were individually matched, the percentages of cases and controls are not necessarily equal in each sex category, because some cases have one matched control and others have more controls. P-values calculated using χ²-tests for categorical variables and Wilcoxon Rank Sum tests for continuous variables.

In this study, hookah smoking and nass chewing were associated with an increased risk of ESCC. Among nass chewers, the ORs (95% CI) for placement of nass under the tongue vs. gingival rim were 3.00 (1.21–7.41) in unadjusted and 0.65 (0.14–3.09) in adjusted models. The association between hookah and nass use and ESCC persisted after excluding ever users of the other product and cigarette smokers (Supplementary Table 2).

**DISCUSSION**

In this study, hookah smoking and nass chewing were associated with approximately two- and three-fold increase, respectively, in the risk of ESCC. The associations between hookah and nass use and ESCC were consistent across different measures of use, including intensity, duration, and cumulative amount of use, and after excluding ever users of the other product and cigarette smokers. This study suggests an increased risk of ESCC associated with ever use of gutka and bidi. However, these associations were based on small number of participants.

A recent meta-analysis has summarised the relatively small number of studies available on long-term effects of hookah use, and has suggested associations between hookah smoking and several health outcomes, including lung cancer and low birth weight (Akl et al, 2010). To our knowledge, there are only three earlier observational studies on the association between hookah smoking and ESCC: two hospital-based case–controls studies from Kashmir Valley and one population-based case–control study from an area with high incidence of ESCC in Iran. One of the studies from Kashmir, with 100 cases and 100 controls, reported prevalence of 36% of hookah use among controls, whereas this prevalence was 92% in cases (P<0.001, based on χ²-tests; Khan et al, 2011). The other study provided an age- and sex-adjusted OR (95% CI) of 21.4 (11.6–39.5) for ever use of hookah, based on 135 cases and 195 controls with hookah-use prevalence of 21% among controls (Malik et al, 2011). In the Iranian study, with 300 ESCC cases and 571 controls, the OR (95% CI) for ever use of hookah was 1.85 (0.95–3.58), adjusted for several socio-demographic factors, but not for other tobacco products use (Nasrollahzadeh et al, 2008). When users of other tobacco products were excluded from the analyses, the OR (95% CI) for hookah use only was 1.69 (0.76–3.79), based on small number of hookah smokers (12 and 18 among ESCC cases and controls, respectively). The higher risk estimates in previous studies from Kashmir Valley may be because of these results, unlike ours, were not adjusted for several potential confounding socio-demographic factors and the use of other tobacco products. Also, in one of those studies, controls were medical staff or those who referred for routine check-ups to SKIMS, many of whom were probably from Srinagar (Malik et al, 2011), which is the only major urban area in the valley. As hookah use is much more common in rural than in urban areas of the valley (Siddiqi and Preussmann, 1989), enrolment of cases who are referred from whole valley, but recruitment of controls mainly from urban areas (selection bias), can be another reason for the above difference in the magnitude of risk estimates.
### Table 2  Association between tobacco and alcohol use and ESCC

| Tobacco use | ESCC cases, N (%) | Matched controls, N (%) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|-------------|-------------------|-------------------------|------------------------|----------------------|
| **Hookah smoking** | | | | |
| Never | 282 (40.2) | 964 (58.0) | Referent | Referent |
| Ever | 420 (59.8) | 699 (42.0) | 2.36 (1.92–2.89) | 1.85 (1.41–2.44) |
| **Intensity** | | | | |
| Never use | 282 (40.2) | 964 (58.0) | Referent | Referent |
| <4 times per day | 76 (10.8) | 179 (10.8) | 1.73 (1.26–2.37) | 1.37 (0.91–2.07) |
| 4–5 times per day | 98 (14.0) | 268 (16.1) | 1.39 (1.04–1.86) | 1.10 (0.69–1.79) |
| ≥6 times per day | 246 (35.0) | 252 (15.1) | 4.35 (3.45–5.66) | 4.02 (2.79–5.78) |
| P for trend | | | <0.001 | <0.001 |
| **Duration** | | | | |
| Never use | 282 (40.2) | 964 (58.0) | Referent | Referent |
| 1–33 years | 120 (17.1) | 198 (11.9) | 2.23 (1.68–2.96) | 1.77 (1.21–2.60) |
| 34–45 years | 147 (20.9) | 276 (16.6) | 2.06 (1.57–2.69) | 1.77 (1.24–2.52) |
| ≥46 years | 153 (21.8) | 223 (13.4) | 2.99 (2.23–4.01) | 2.06 (1.42–3.01) |
| P for trend | | | <0.001 | <0.001 |
| **Cumulative use** | | | | |
| Never use | 282 (40.2) | 964 (58.0) | Referent | Referent |
| 1–139 hookah-years | 97 (13.8) | 228 (13.7) | 1.66 (1.24–2.21) | 1.12 (0.77–1.64) |
| 140–240 hookah-years | 110 (15.7) | 245 (14.8) | 1.77 (1.33–2.36) | 1.54 (1.05–2.26) |
| ≥241 hookah-years | 213 (30.3) | 252 (15.1) | 4.35 (3.45–5.66) | 4.02 (2.79–5.78) |
| P for trend | | | <0.001 | <0.001 |
| **Frequency of changing water** | | | | |
| Daily | 388 (92.4) | 656 (94.5) | Referent | Referent |
| Weekly | 32 (7.6) | 38 (5.5) | 1.48 (0.84–2.60) | 1.32 (0.57–3.02) |
| **Gutka chewing** | | | | |
| Never | 692 (99.6) | 1650 (99.2) | Referent | Referent |
| Ever | 10 (1.4) | 13 (0.8) | 1.84 (0.80–4.23) | 2.87 (0.87–9.46) |
| **Nass chewing** | | | | |
| Never | 501 (71.4) | 1471 (88.5) | Referent | Referent |
| Ever | 201 (28.6) | 192 (11.5) | 3.41 (2.67–4.37) | 2.88 (2.06–4.04) |
| **Intensity** | | | | |
| Never use | 501 (71.4) | 1471 (88.5) | Referent | Referent |
| <4 times per day | 40 (5.7) | 71 (4.3) | 2.04 (1.34–3.12) | 1.61 (0.93–2.77) |
| 4–5 times per day | 54 (7.7) | 74 (4.4) | 2.28 (1.56–3.34) | 2.25 (1.34–3.80) |
| ≥6 times per day | 107 (15.2) | 47 (2.8) | 6.87 (4.70–10.03) | 5.34 (3.24–8.83) |
| P for trend | | | <0.001 | <0.001 |
| **Duration** | | | | |
| Never use | 501 (71.6) | 1471 (88.4) | Referent | Referent |
| 1–34 years | 63 (9.0) | 62 (3.7) | 3.41 (2.28–5.09) | 2.42 (1.41–4.17) |
| 35–44 years | 39 (5.6) | 50 (3.0) | 2.41 (1.52–3.80) | 2.19 (1.17–4.08) |
| ≥45 years | 97 (13.8) | 80 (4.8) | 4.02 (2.83–5.71) | 3.58 (2.20–5.82) |
| P for trend | | | <0.001 | <0.001 |
| **Cumulative use** | | | | |
| Never use | 501 (71.6) | 1471 (88.5) | Referent | Referent |
| 1–119 nass-years | 46 (6.5) | 52 (3.1) | 2.93 (1.91–4.50) | 2.14 (1.20–3.82) |
| 120–199 nass-years | 36 (5.1) | 71 (4.3) | 1.70 (1.10–2.61) | 1.44 (0.80–2.60) |
| ≥200 nass-years | 117 (16.7) | 69 (4.1) | 5.31 (3.78–7.45) | 4.56 (2.89–7.22) |
| P for trend | | | <0.001 | <0.001 |
| **Site of placement of nass/gutka in the mouth** | | | | |
| Gingival rim | 149 (74.1) | 166 (86.5) | Referent | Referent |
| Under the tongue | 52 (25.9) | 26 (13.5) | 3.00 (1.21–7.41) | 0.65 (0.14–3.09) |
| **Cigarette smoking** | | | | |
| Never | 632 (90.0) | 1437 (86.4) | Referent | Referent |
| Ever | 70 (10.0) | 226 (13.6) | 0.67 (0.49–0.91) | 0.97 (0.60–1.55) |
| **Intensity** | | | | |
| Never use | 632 (90.0) | 1437 (86.4) | Referent | Referent |
| <5 cigarettes per day | 28 (4.0) | 84 (5.1) | 0.73 (0.46–1.16) | 0.99 (0.50–1.97) |
| 5–6 cigarettes per day | 17 (2.4) | 72 (4.3) | 0.48 (0.28–0.85) | 0.75 (0.34–1.68) |
| ≥7 cigarettes per day | 25 (3.6) | 70 (4.2) | 0.80 (0.49–1.31) | 1.27 (0.55–2.92) |
| P for trend | | | 0.03 | 0.95 |
| **Duration** | | | | |
| Never use | 632 (90.0) | 1437 (86.4) | Referent | Referent |
| 1–29 years | 18 (2.6) | 69 (4.1) | 0.56 (0.32–0.98) | 1.20 (0.51–2.82) |
| 30–39 years | 21 (3.0) | 66 (4.0) | 0.67 (0.39–1.13) | 1.08 (0.47–2.45) |
| ≥40 years | 312 (44.8) | 91 (5.5) | 0.74 (0.47–1.14) | 0.81 (0.42–1.58) |
| P for trend | | | 0.01 | 0.69 |
Hookah smokers seem to be exposed to many toxic compounds as cigarette smokers, such as nicotine, nitric oxide, carbon monoxide, polycyclic aromatic hydrocarbons, and nitrosamines (Monzer et al, 2008; Eissenberg and Shihadeh, 2009; Ghasemi et al, 2010; Jacob et al, 2011). Furthermore, hookah smokers may be exposed to harmful smoke from the burning charcoal (Monzer et al, 2008). The exposure to smoke per puff with hookah smoking may even be higher than with cigarette smoking; each puff from the hookah has reported to deliver 12 times as much smoke as a single cigarette puff (Eissenberg and Shihadeh, 2009). The similarity of biological consequences of waterpipe and cigarette smoking reported in other studies supports the association between hookah and ESCC. The relatively high prevalence of hookah use among the young people in a number of populations worldwide, which is reported to be increasing (Jackson and Aveyard, 2008; Jawaid et al, 2008; Jordan and Delnevo, 2010; Mazia, 2011; Smith et al, 2011; Jarrett et al, 2012), indicates public health implication of this association and other hookah-related adverse health consequences. In our study, less frequent changing of water in hookah apparatus was not associated with ESCC risk. However, the number of hookah smokers who changed the water less frequently than daily was small.

An association between nass use and precancerous oral and oesophageal lesions (Zaridze et al, 1986; Evstifeeva and Zaridze, 1992) and ESCC (Nasrollahzadeh et al, 2008) has been reported in a few studies. The latter study reported a two-fold increased risk of ESCC in ever- vs never-nass users (Nasrollahzadeh et al, 2008). The association between nass chewing and ESCC is plausible, because several experimental and epidemiological studies have shown the role of chewing tobacco in oesophageal carcinogenesis (IARC Working Group, 2007, 2012). Furthermore, other constituents of nass, such as polycyclic aromatic hydrocarbons from ash, may have additional carcinogenic effects on the oesophageal epithelium (Roth et al, 1998; Islami et al, 2009; Abedi-Ardekani et al, 2010). We did not find any association between placement location of nass in the mouth and ESCC risk in adjusted models.

Although cigarette smoking increases ESCC risk by 3- to 5-fold in western countries (Tuyns, 1983; Brown et al, 2001), it has been associated with only 1.3- to 1.5-fold increased risk in high-incidence areas of China and Iran (Tran et al, 2005; Nasrollahzadeh et al, 2008), suggesting that the majority of ESCC cases in those high-incidence areas are due to other factors. In our study, the highest category of cumulative use showed a non-significant OR of 1.27. This may partly be related to low cumulative cigarette use in our study; only 2.2% of participants had smoked 20 or more pack-years of cigarettes. The association between bidi smoking and ESCC has been reported by several other studies from areas where this habit is more common (IARC Working Group, 2012); our study provides only modest supporting evidence.

This study is the largest study from Kashmir Valley that has investigated risk factors of ESCC in this relatively high-risk region, using analytical methods and with adjustments for several potential confounding factors, and the largest study that has ever studied the association between hookah and nass use and ESCC. Other strengths of this study include matching controls to all cases for the district of residence, to reduce possibility of confounding by area of residence, using several measures of exposure for common tobacco products, and histological confirmation of all ESCC diagnoses. Because of its case–control design, recall bias can be a limitation of this study. As the majority of participants had little formal education, and because there was little earlier information on the association between hookah and nass use and risk of ESCC, participants were unlikely to be aware of study hypotheses, particularly with regard to hookah and nass. Therefore, it is unlikely that the use of these products were reported differentially by controls and ESCC cases. Also, the evidence for recall bias in retrospective vs prospective epidemiologic studies is generally weaker for tobacco products than for other cancer risk factors (Gandini et al, 2008).

In conclusion, this study shows that hookah and nass use are associated with an increased risk of ESCC. These associations, as well as the associations between these products and several other health outcomes, indicate that the tobacco control programmes should more strictly include tobacco products other than cigarette. Because of the increasing trend of using hookah reported worldwide, results of this study can have public health implications not only for the regions in which hookah use has been a tradition, but also for many other regions, including the western countries.

Table 2 (Continued)

| Tobacco use | ESCC cases, N (%) | Matched controls, N (%) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|-------------|------------------|-------------------------|----------------------|----------------------|
| Cumulative use |                   |                         |                      |                      |
| Never use   | 632 (90.0)       | 1437 (86.4)             | Referent             | Referent             |
| 1–6.2 pack-years | 23 (3.3)       | 77 (4.6)                | 0.63 (0.39–1.04)     | 1.30 (0.62–2.71)     |
| 6.3–13.1 pack-years | 21 (3.0)      | 73 (4.4)                | 0.61 (0.37–1.02)     | 0.59 (0.28–1.25)     |
| ≥ 13.2 pack-years | 26 (3.7)       | 76 (4.6)                | 0.75 (0.47–1.21)     | 1.27 (0.56–2.86)     |
| P for trend |                   |                         |                      |                      |
| Bid smoking |                   |                         |                      |                      |
| Never use   | 687 (97.9)       | 1660 (99.8)             | Referent             | Referent             |
| Ever use    | 15 (2.1)         | 3 (0.2)                 | 11.82 (3.40–41.06)   | 16.30 (2.46–108.20)  |
| Alcohol drinking |             |                         |                      |                      |
| Never use   | 694 (98.9)       | 1663 (100)              | Referent             | Referent             |
| Ever use    | 8 (1.1)          | 0 (0.0)                 | —                    | —                    |

Abbreviations: CI = confidence interval; ESCC = oesophageal squamous cell carcinoma; OR = odds ratio. ORs (95% CIs) were obtained from conditional logistic regression models. P for trend was obtained from the same models by assigning consecutive numbers to categories within each categorical variable. Cumulative use was calculated by multiplying intensity of use (per day) by duration of use (in years). Numbers may not add up to the total numbers due to missing data in some variables. Adjusted ORs (95% CIs) were obtained from models in which age, ethnicity, religion, place of residence, education level, cumulative use of cigarette, hookah and nass, and ever use of bidi, cannabis, gutka, and alcohol, and daily fruit and fresh vegetable consumption were included. The ORs (95% CIs) for intensity and duration of nass, hookah, and cigarette use were not adjusted for cumulative use of the respective tobacco product.
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Conflict of interest

The authors declare no conflict of interest.