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Nass use, Cigarette Smoking, Alcohol Consumption and Risk of Oral and Oesophageal Precancer

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In a cross sectional study, conducted in Uzbekistan, an area with a high incidence of oral and oesophageal cancer, 1569 men were interviewed regarding use of nass quid, cigarette smoking and alcohol drinking. All subjects in the study had an oral examination, and oesophagoscopy was performed in 1344 men. Nass use and cigarette smoking emerged as independent risk factors for oral leukoplakia. The prevalence odds ratio (OR) for life-time nass intake equivalent rose from 1.0 in never-users to 5.17 [95% confidence interval (CI), 3.10–8.61] in the highest category; for total pack-years of cigarettes smoked the risk rose from 1.0 in never-smokers to 10.03 (95% CI, 4.9–20.6) in the highest category. There was a significant trend in risk ($P < 0.001$), for both factors. In the group with oral leukoplakia, the effect of nass use and cigarette smoking appeared to be additive. Cigarette smoking was also found to be an independent risk factor for oesophageal lesions and was significantly associated with chronic oesophagitis. The risk of chronic oesophagitis in the group with the highest pack-years of cigarettes smoked was approximately double that among non-smokers [Odds ratio (OR) = 2.47; 95% CI 1.34–4.56]. There was a weak association between nass use and oesophageal pathology: the highest life-time intake equivalent was associated with an OR of 1.56 (95% CI 1.09–2.23). Alcohol intake was not found to be independently associated with the presence of oral and oesophageal precancerous lesions.
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INTRODUCTION

THE INCIDENCE of oral cancer is higher in Central Asia than in other parts of the former Soviet Union. However, within Central Asia, incidence rates of oral cancer differs substantially in different regions, this being associated, probably, with local differences in the prevalence of smokeless tobacco use [1].

The high levels of oral cancer in the Central Asian Republics are thought to be attributable to nass quid use. Nass usually contains tobacco, ash, cotton oil and/or sesame oil and lime. Whereas it is known that the use of smokeless tobacco is associated with oral cancer [2], the epidemiological evidence on nass use and oral cancer is not sufficient to confirm the causality of this association.

Cigarette smoking has been shown to increase the risk of oral cancer. The results of both cohort and case control studies carried out mainly in North America and Europe have shown that cigarette smoking significantly increases the risk of oral cancer [3]. Alcohol has also been demonstrated to be a risk factor for oral cancer, acting on its own as well as synergistically with smoking [4].

Evidence has been accumulating suggesting that oral leukoplakia can be a precursor of oral cancer [5]. A high prevalence of oral leukoplakia has been observed in areas with high incidence of oral cancer. An increase in the prevalence of oral leukoplakia was observed among users of different types of tobacco mixtures and betel quid. It has been observed that the most frequent site of oral leukoplakia and cancer is the site in the mouth where tobacco-containing quid is placed [5–7].

The Central Asian Republics also have very high rates of oesophageal cancer, reaching, in some areas, rates comparable with the highest rates in China and Iran [8]. For example, age-standardised (World Standard Population) incidence rates per 100 000 person-years in the Muinak Region of Karakalpakstan (Uzbekistan) for males are 125.0 and for females 150.7 [9].

The epidemiological studies carried out in the USA and Europe suggest that the most important risk factors for oesophageal cancer in these regions are smoking and alcohol consumption [3, 4]. However, the causes of oesophageal cancer in areas with very high incidence, such as Iran, China and Russia are not so clear [8], although several factors, such as lack of consumption of food rich in vitamins, drinking of hot tea and use of opium, have been implicated [6, 8, 10]. There is also some evidence that the high incidence of oesophageal cancer could also be related to betel quid chewing [2].

Studies in Linxian (China) suggest that the high incidence of oesophageal cancer in this area could be related to the consumption of pickled vegetables and mouldy foods, some of which have been shown to be mutagenic, silica contamination of millet, ingestion of foods with high levels of nitrosamines and endogenous formation of nitrosamines [11].

It has been suggested, that chronic oesophagitis is a precursor of oesophageal cancer. A high prevalence of chronic

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Table 1. Risk of oral leukoplakia and preleukoplakia associated with use of nass

	Case	Control*	ORc†	ORa‡	(95% CI)	P§
Never	66	282	1.00	1.00		
Ever-used	125	184	2.90	3.80	(2.57–5.61)	
Ex-users	7	13	2.30	3.00	(1.08–8.32)	
Current users	118	171	2.95	3.86	(2.60–5.72)	
Age started (in years)‖						
⩾31	33	57	2.47	3.03	(1.76–5.20)	
(24–30)	26	56	1.98	2.72	(1.53–4.83)	
⩽23	59	58	4.35	5.79	(3.54–9.48)	0.027
Years used‖						
⩽28	34	60	2.42	2.93	(1.71–5.02)	
(29–38)	30	57	2.25	2.90	(1.65–5.08)	
(39–60)	54	54	4.27	5.95	(3.58–9.89)	<0.001
Times/day‖ ¶						
⩽7	33	64	2.20	2.79	(1.63–4.76)	
(8–11)	35	53	2.82	3.96	(2.30–6.83)	
(12–20)	48	54	3.80	4.87	(2.92–8.13)	<0.001
Life-intake equivalent‖ ¶						
⩽154	23	57	1.72	1.94	(1.07–3.51)	
(155–396)	44	59	3.19	4.64	(2.77–7.80)	
(397–1160)	49	55	3.81	5.17	(3.10–8.61)	<0.001
Years stopped¶ using						
>10	4	6	2.85	3.17	(0.78–12.84)	
(10–26)	3	5	2.56	3.98	(0.88–17.92)	0.172

Baseline group in all sections is "never use".
*Reference group—men with no abnormality on either oesophagoscopy or oral examination.
†Crude OR.
‡By logistic regression analysis adjusted for smoking, alcohol drinking and age.
§Two-tailed *P* values for linear trend test by conditional logistic regression with all the confounding variables for OR in the model.
‖Restricted analysis among current nass users.
¶The numbers do not equal the total shown due to missing values.

oesophagitis has been reported from areas with high incidence of oesophageal cancer [6, 12–14].

Investigation of the possible relationship between nass use, cigarette smoking and alcohol consumption, and the prevalence of oral leukoplakia and chronic oesophagitis is presented in this article.

MATERIALS AND METHODS

Comparison groups

Male residents of nine villages in one local authority district in the Samarkand Oblast of Uzbekistan were invited to attend a medical examination. All 1 569 men were interviewed and had an oral examination; 1 344 men had oesophagoscopy. The results of these examinations were used to define comparison groups used in the statistical analysis.

Case groups are defined as having (1) oral leukoplakia, and (2) chronic oesophagitis. The definitions of oral leukoplakia and chronic oesophagitis used in the survey have been described in detail elsewhere [5, 6, 7, 14]. The control group was defined as consisting of subjects free of both oral and oesophageal lesions.

Age-standardised (World Standard Population) incidence rates per 100 000 person-years in men for oral and oesophageal cancer are 8.0 and 45.0, respectively.

The case group for chronic oesophagitis included 680 subjects and the case group for oral leukoplakia 191 subjects. The control groups included 466 men who had neither oral leukoplakia, nor chronic oesophagitis.

Measurement of exposure

All participants were directly interviewed using a structured questionnaire. The questions regarding nass use and cigarette consumption included age at first use, duration of use, frequency of use at the time of interview and, for nass use, the site of the mouth where the quid is usually placed.

Information was collected on alcohol consumption, including the type of alcoholic beverage drunk (beer, wine or strong liquors, such as vodka, etc.). The amount of alcohol (in grams) consumed per month at the time of interview was calculated.

Other information regarding date of birth, place of birth, place of residence, ethnic group, medical history (including current symptomatology and family history of cancer) was also obtained.

Data analysis

Nass use was examined both in terms of the average frequency of use per day and the estimated life-time intake equivalent used, calculated as reported daily frequency at the time of interview multiplied by years of use (by analogy with pack-years for cigarettes).

Cigarette smoking was examined both in terms of the average number of cigarettes smoked per day at the time of interview and the estimated pack-years smoked. The total pack-years smoked was calculated to be the average number of packs consumed per day multiplied by the number of years that this amount was smoked: one pack-year is equivalent to 7300 cigarettes smoked.

Table 2. Risk of chronic oesophagitis associated with use of nass

	Case	Control*	ORc†	ORa‡	(95% CI)	P§
Never	380	282	1.00	1.00		
Ever-used	298	184	1.20	1.28	(1.00–1.63)	
Ex-users	25	13	1.43	1.51	(0.74–3.09)	
Current	273	171	1.18	1.27	(0.98–1.62)	
Age started (in years)‖						
⩾31	92	57	1.20	1.24	(0.86–1.80)	
(24–30)	72	56	0.95	1.03	(0.70–1.52)	
⩽23	108	58	1.38	1.48	(1.03–2.11)	0.23
Years used‖¶						
⩽28	88	60	1.09	1.14	(0.79–1.65)	
(29–38)	75	57	0.98	1.05	(0.72–1.54)	
(39–60)	109	54	1.50	1.59	(1.10–2.30)	0.003
Times/day‖¶						
⩽7	90	64	1.04	1.12	(0.78–1.61)	
(8–11)	78	53	1.09	1.19	(0.80–1.75)	
(12–20)	103	54	1.42	1.46	(1.01–2.10)	0.018
Life-intake equivalent‖¶						
⩽154	64	57	0.83	0.85	(0.57–1.26)	
(155–396)	109	59	1.37	1.56	(1.09–2.23)	
(397–780)	98	55	1.32	1.35	(0.93–1.95)	0.01
Years stopped using¶						
>5	13	6	1.50	1.56	(0.57–4.30)	
⩽5	10	5	1.39	1.50	(0.50–4.50)	0.58

Baseline group in all sections is "never use".
*Reference group—men with no abnormality on either oesophagoscopy or oral examination.
†Crude OR.
‡By logistic regression analysis adjusted for smoking, alcohol drinking and age.
§Two-tailed *P* values for linear trend test by conditional logistic regression with all the confounding variables for OR in the model.
‖Restricted analysis among current nass users.
¶The numbers do not equal the total shown due to missing values.

The average monthly consumption of alcohol in grams was calculated by taking into account the amount drunk per month of each type of alcoholic beverage. For these analyses, grams of beer, wine and hard drinks were converted into grams of alcohol in accordance with the approximate ratio of alcohol contents in beverages in the region investigated as follows: grams of beer were multiplied by 0.04, grams of wine by 0.12 and of strong drinks by 0.40.

Although alcohol intake was found not to be a risk factor for oral and oesophageal precancer, a term for alcohol intake was included in all the logistic regression models because of its known association with oral and oesophageal cancer.

Continuous variables were categorised into three groups using the tertiles of the control group. The prevalence odds ratios (OR) were computed to estimate the risk of oral and oesophageal precancer associated with nass use, cigarette smoking and alcohol drinking: unless otherwise specified, values in parentheses following an OR in the text are the lower and upper bounds of the 95% confidence interval (CI). The crude ORs and the corresponding 95% CIs were calculated by using the Mantel–Haenszel method for each level of the exposure of interest [15]. Logistic regression was used to adjust for potential confounding [16].

Formal statistical assessment of the effect modification between cigarette smoking and nass use, cigarette smoking and alcohol drinking, alcohol drinking and nass use was conducted using unconditional logistic regression. Tests for trend were performed by treating each variable in the model as a continuous variable rather than several indicator variables: the ratio of the estimated coefficient to its standard error obtained from the model was used to make statistical inferences based upon a two-sided alternative hypothesis at the 5% level. Although no significant association between age and oesophageal or oral precancer was found, a term for age in three categories (tertiles) was included in all logistic regression models.

Data preparation and preliminary descriptive statistical analysis was performed using the SAS package [17]. Data analysis by logistic regression was carried out using the SEARCH Package [18].

RESULTS

Background information

The distributions of age, ethnicity and place of birth were similar between the main study groups. The frequency distribution of place of residence (nine different villages), was again similar between the groups. Uzbek ethnics represented 80% of the group with oral lesions only, 92% with oesophageal lesions only and 91% of the control group. The great majority of men in the study were born in their present place of residence: 78% with oral lesions, 90% with oesophageal lesions and 91% in the control group. All men in the study were farmers, members of collective farms, specialising in cotton growth.

No risk associated with age was found, but an age variable was present in all regression models used.

Table 3. Risk of oral leukoplakia associated with smoking

	Case	Control*	ORc†	ORa‡	(95% CI)	P§
Never	116	377	1.00	1.00		
Ever-used	75	88	2.77	3.54	(2.33–5.38)	
Ex-smokers	13	37	1.14	1.07	(0.52–2.18)	
Current	62	51	3.95	6.02	(3.70–9.80)	
Age started (in years)‖¶						
⩾28	33	25	4.29	6.63	(3.54–12.42)	
(21–27)	14	10	4.55	7.63	(3.13–18.59)	
⩽20	14	16	2.84	4.06	(1.81–9.07)	0.25
Years smoking‖¶						
⩽30	16	18	2.89	4.13	(1.93–8.87)	
(31–42)	27	19	4.62	7.45	(3.73–14.88)	
⩾43	18	14	4.18	6.58	(2.99–14.48)	<0.001
Cigarettes (per day)‖						
⩽4	11	17	2.10	1.89	(0.82–4.36)	
(5–19)	25	16	5.08	9.18	(4.45–18.96)	
=20	23	15	4.98	10.30	(4.87–21.81)	
(21–40)	3	3	3.25	4.89	(0.88–27.17)	<0.001
Pack-years‖¶						
⩽7	18	17	3.27	3.81	(1.80–8.04)	
(8–30)	17	19	2.76	4.51	(2.17–9.37)	
(31–96)	26	15	5.36	10.03	(4.88–20.61)	<0.001
Years stopped smoking¶‖						
⩾21	7	20	1.14	1.13	(0.44–2.91)	
⩽21	6	13	1.50	1.33	(0.46–3.81)	0.038

Baseline group in all sections is 'never smokers'.
*Reference group—men with no abnormality on either oesophagoscopy or oral examination.
†Crude OR.
‡By logistic regression analysis adjusted for nass use, alcohol drinking and age.
§Two-tailed *P* values for linear trend test by conditional logistic regression with all the confounding variables for OR in the model.
‖Restricted analysis among current smokers.
¶The numbers do not equal the total shown due to missing values.

Nass use and the risk of oral lesions (*Table* 1)

Use of nass was significantly associated with the risk of oral leukoplakia. The risk was significantly increased in all three groups studied: in ever-users (OR = 3.8; 95% CI 2.57–5.61), ex-users (OR = 3.00; 95% CI 1.08–8.32) and current users (OR = 3.86; 95% CI 2.60–5.72). Age at which nass use started was significantly associated with the risk of oral leukoplakia with a statistically significant trend ($P = 0.027$) and with the highest risk (OR = 5.79; 95% CI 3.54–9.48) for men who started quid use before the age of 23 years. Duration of use also turned out to be a significant determinant of the risk of oral precancerous lesion, with a statistically significant trend ($P < 0.001$). The highest risk (OR = 5.95; 95% CI 3.58–9.89) was observed in men who used nass for more than 39 years. Daily frequency of use has also been found to be associated with the risk of oral leukoplakia. The highest risk (OR = 4.87; 95% CI 2.92–8.13) was observed in men using nass 12–20 times/day, in comparison with an OR of 2.79 (95% CI 1.63–4.76) among those who used nass less than 8 times/day and an OR of 3.96 (95% CI 2.30–6.83) for men using nass 8–11 times/day with a highly significant trend ($P < 0.001$).

Risk estimates for lifetime nass intake equivalent use also demonstrated a dose–response relationship between the latter variable and the risk of oral leukoplakia with a statistically significant trend ($P < 0.001$). The highest lifetime intake equivalent (397–780) produced an OR of 5.17 (95% CI 3.10–8.61), whilst the lowest lifetime intake equivalent (less than 155) gave an OR = 1.94 (95% CI 1.07–3.51).

There was no difference in the risk of oral leukoplakia among those who stopped using nass less than 9 years ago compared with those who stopped 10–26 years ago. It should be noted, however, that both comparison groups were very small.

Nass use and the risk of oesophageal lesions (*Table* 2)

The association between nass use and the risk of chronic oesophagitis was found to be weak, although statistically significant increases in risk were observed in men who started using nass before the age of 24 years (OR = 1.48; 95% CI 1.03–2.11), who used nass for more than 39 years (OR = 1.59; 95% CI 1.10–2.30), who used nass 12–20 times/day (OR = 1.46; 95% CI 1.01–2.10), and finally for men whose life-intake equivalent of nass was 155–396 times/life (OR = 1.56; 95% CI 1.09–2.23). A statistically significant trend was observed in relation to the following variables: years used ($P = 0.0003$), times/day ($P = 0.018$), life-intake equivalent ($P = 0.01$). The duration since giving up nass use did not influence the risk of oesophageal lesions.

Smoking and the risk of oral leukoplakia (*Table* 3)

Smoking was found to substantially increase the risk of oral leukoplakia: a statistically significant increase in risk was observed among men who had ever smoked (OR = 3.54; 95% CI 2.33–5.38) and current smokers (OR = 6.02; 95% CI 3.70–9.80) and the risk was not increased in ex-smokers. There was no statistically significant association between the age that

Table 4. Risk of chronic oesophagitis associated with smoking

	Case	Control*	ORc†	ORa‡	(95% CI)	P§
Never	492	377	1.00	1.00		
Ever-used	186	88	1.62	1.60	(1.19–2.16)	
Ex-smokers	67	37	1.39	1.32	(0.85–2.04)	
Current users	119	51	1.79	1.82	(1.26–2.62)	
Age started (in years)‖						
⩾28	27	16	1.29	1.33	(0.70–2.52)	
(21–27)	25	10	1.92	1.84	(0.86–3.91)	
⩽20	67	25	2.05	2.12	(1.30–3.46)	<0.001
Years smoking‖						
⩽30	24	18	1.02	1.08	(0.57–2.03)	
(31–42)	55	19	2.22	2.21	(1.28–3.83)	
⩾43	40	14	2.19	2.20	(1.17–4.15)	<0.001
Cigarettes (per day)‖¶						
⩽4	32	17	1.44	1.36	(0.74–2.50)	
(5–19)	42	16	2.01	1.98	(1.09–3.61)	
=20	32	15	1.63	1.62	(0.86–3.05)	
(21–40)	10	3	2.55	2.64	(0.72–9.75)	0.009
Pack-years‖¶						
⩽7	31	18	1.32	1.26	(0.69–2.30)	
(8–30)	41	18	1.75	1.82	(1.02–3.27)	
(31–108)	44	15	2.25	2.47	(1.34–4.56)	0.014
Years stopped smoking¶						
>14	31	16	1.43	1.33	(0.46–3.81)	
⩽14	31	17	1.08	1.13	(0.44–2.91)	0.40

Baseline group in all sections is "never smokers".
*Reference group—men with no abnormality on either oesophagoscopy or oral examination.
†Crude OR.
‡By logistic regression analysis adjusted for nass use, alcohol drinking and age.
§Two-tailed *P* values for linear trend test by conditional logistic regression with all the confounding variables for OR in the model.
‖All results for current smokers.
¶The numbers do not equal the total shown due to missing values.

Table 5. Risk of oral leukoplakia associated with alcohol

	Case	Control*	ORc†	ORa‡	(95% CI)
Never¶	68	168	1.00	1.00	
Ever-used¶	116	260	1.11	0.85	(0.57–1.27)
Ex-drinkers	20	47	1.06	0.92	(0.48–1.76)
Current	96	213	1.12	0.83	(0.55–1.27)
Type of alcohol§‖					
Beer/wine only	2	2	—	—	
Liquor only	80	193	1.03	0.81	(0.52–1.25)
Mixed	13	16	2.02	1.02	(0.42–2.49)
Spirit equivalent (per month)§‖					
⩽200	27	67	1.00	0.95	(0.55–1.65)
(200–350)	29	70	1.03	0.78	(0.45–1.35)
(350–2400)	39	74	1.31	0.84	(0.51–1.40)

Baseline group in all sections is "never alcohol drinkers".
*Reference group—men with no abnormality on either oesophagoscopy or oral examination.
†Crude OR.
‡By logistic regression analysis adjusted for nass use, smoking and age.
§Restricted analysis among current drinkers.
‖The numbers do not equal the total shown due to missing values.

smoking started and the risk of oral cancer, although risk estimates were high and statistically significant for all three levels of this variable: OR = 6.63; (95% CI 3.54–12.42) for men who started smoking after 27 years of age, OR = 7.63; (95% CI 3.31–18.59)—who started smoking between 21–27 years of age and OR = 4.06; (95% CI 1.81–9.07)—who started smoking before the age of 20 years.

Duration of smoking in years was found to be associated with the risk of oral cancer, the risk apparently increasing with increased dose, with a statistically significant trend

Table 6. Risk of chronic oesophagitis associated with alcohol

	Case	Control*	ORc†	ORa	(95% CI)‡
Never‖	219	169	1.00	1.00	
Ever-used‖	402	260	1.19	1.13	(0.86–1.49)
Ex-drinkers	61	47	1.00	0.96	(0.62–1.50)
Current	341	213	1.24	1.18	(0.89–1.56)
Type of alcohol§‖					
Beer/wine only	2	2			
Liquor only	308	193	1.23	1.19	(0.89–1.59)
Mixed	27	16	1.30	1.05	(0.54–2.07)
Spirit equivalent (per month)§‖					
≤200	140	67	1.61	1.54	(0.55–1.65)
(201–350)	100	70	1.10	1.03	(0.45–1.35)
(351–2400)	97	74	1.01	1.07	(0.51–1.40)

Baseline group in all sections is "never alcohol drinkers".
*Reference group—men with no abnormality on either oesophagoscopy or oral examination.
†Crude OR.
‡By logistic regression analysis adjusted for nass use, smoking and age.
§Restricted analysis among current drinkers.
‖The numbers do not equal the total shown due to missing values.

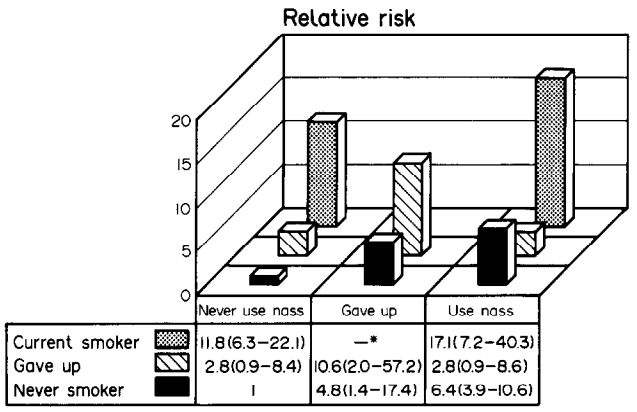

Fig. 1. Cigarette smoking and nass use interaction table. *Not enough data to estimate the risk. By logistic regression adjusted for age and alcohol.

($P<0.001$). The same was found for the number of cigarettes smoked per day ($P<0.001$). Risk of oral leukoplakia increased significantly with increase in estimated pack-years of cigarettes consumed from less than 3.81 (95% CI 1.80–8.04) for less than 7 pack-years, to 10.03 (95% CI 4.88–20.61) for more than 31 pack-years, with a statistically significant trend ($P<0.01$). Giving up smoking 21 years or more ago, or for less than 21 years ago gave estimates of OR which were significantly different from each other ($P=0.0038$); risk of oral precancer being 1.13 (95% 0.44–2.91) for men who gave up smoking 21 years or more ago, and 1.33 (95% CI 0.46–3.81) for men who gave up less than 21 years ago.

Smoking and the risk of oesophageal lesions (Table 4)

Smoking was found to increase the risk of oesophageal cancer: the risk being significantly increased in ever-smokers (OR = 1.60; 95% CI 1.19–2.16) and current smokers (OR = 1.82; 95% CI 1.26–2.62). The age at which smoking started was significantly associated with the risk of oesophageal lesions in a dose–response fashion with a statistically significant trend ($P<0.001$). For those who started smoking at the earliest age (≤20 years), the relative risk was the highest (OR = 2.12; 95% CI 1.30–3.46). The duration of smoking significantly increased the risk of oesophageal precancerous lesions, with a significant trend ($P<0.001$). Risk estimates increased significantly with an increase in the number of cigarettes smoked per day ($P=0.009$) and pack-years ($P=0.014$).

Alcohol consumption and the risk of oral leukoplakia and chronic oesophagitis (Tables 5 and 6).

Alcohol consumption did not alter the risk of oral leukoplakia. Risk estimates were close to unity for consumption of all types of alcohol (beer, wine, spirits), at all doses (Table 5). No association was observed between alcohol consumption and the risk of chronic oesophagitis (Table 6).

Combined effect of nass use and smoking on the risk of oral leukoplakia and chronic oesophagitis (Fig. 1).

Figure 1 presents the results of the analysis of the association between risk of oral precancerous lesions and the use of nass and cigarette smoking, by logistic regression adjusted for age and alcohol consumption. The relative risk of oral leukoplakia among nass users who had ever smoked was 6.41 (95% CI 3.89–10.55), in current smokers who had never used nass 11.81 (95% CI 6.32–22.07), while, in current smokers who used nass, the relative risk estimates were highest (OR = 17.06; 95% CI 7.23–40.27), suggesting an additive effect on risk of oral leukoplakia of these two tobacco-using habits. Similar analysis for chronic oesophagitis did not reveal an interaction between nass use and smoking.

DISCUSSION

The results of this study, that use of nass quid and cigarette smoking are associated with the risk of oral leukoplakia, support the existing evidence that both smokeless tobacco use and cigarette smoking increase the risk of oral cancer [2, 3].

The stronger effect of smoking in comparison with nass use on the risk of oral precancer could be explained by low levels in nass of tobacco-specific *N*-nitrosocompounds [6, 7] compared with those in other types of commercial chewing tobacco and snuff [19, 20]. The low levels of *N*-nitrosamines

in nass are not surprising because, contrary to commercially produced chewing tobacco, which is a highly processed product with long aging and fermentation procedures, nass production requires only a short aging process. However, the analysis of nass samples for mutagenicity has shown that nass contains chemicals that exert a genotoxic effect without enzymatic activation [6].

Contrary to the probable low carcinogenicity of nass, cigarettes produced and sold in this area, as well as in other regions of the former Soviet Union, are very high in tar and nicotine [7]. However, the high prevalence of nass use and the low prevalence of smoking in this area suggest that nass still remains probably the most important risk factor for oral cancer. In this survey a remarkably high proportion of men used nass (44%), while only 25% smoked cigarettes. However, this may be changing with an increase in cigarette smoking among the population of this area.

The most important risk factor for oesophageal precancerous lesions in this study was cigarette smoking. However, if compared with oral leukoplakia, risk estimates were lower.

Nass use was associated with a very small increase in the risk of chronic oesophagitis. However, taking into account that a very high proportion of men living in the area used nass, the attributable risk for nass use may not be small.

In this study alcohol consumption was found not to affect the risk of either oral leukoplakia or chronic oesophagitis, suggesting that this habit does not contribute to increased risk of oral and oesophageal cancer in this area. This is contrary to observations in studies in North America and Europe, where alcohol consumption was associated with high risk of oral and oesophageal cancer. Wynder *et al.* [21] and Rothman and Keller [22] concluded that about three-quarters of the cases of oral cancer in the population of the USA could have been prevented had exposure to alcohol and tobacco not occurred.

In a case-control study in the USA by Wynder and Bross [23], alcohol and tobacco appeared to combine multiplicatively to increase the risk of oesophageal cancer, and the total proportion of the risk attributable to the two factors together was 75%. Case-control studies conducted in Northern France [24] confirmed these findings; these studies indicate a dominant effect of alcohol at high exposure levels.

The findings from this study also suggest that the main causes of oral leukoplakia and cancer in the Central Asian republics of the former Soviet Union are, respectively the use of nass and cigarette smoking. Although cigarette smoking and nass use are, most probably, involved in the causation of chronic oesophagitis and oesophageal cancer, the high prevalence of both of these diseases could not be attributed to these two habits only.

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