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Poor oral hygiene and risk of esophageal squamous cell carcinoma in Kashmir

N A Dar*[,1,2], F Islami[2,3], G A Bhat[1], I A Shah[1], M A Makhdoomi[1], B Iqbal[1], R Rafiq[1], M M Lone[4], C C Abnet[5] and P Boffetta[2,6]

[1]Department of Biochemistry, University of Kashmir, Hazratbal Srinagar, JK 190006, India; [2]The Tisch Cancer Institute and Institute for Transitional Epidemiology, Mount Sinai School of Medicine, New York, NY 10029, USA; [3]Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran 14117, Iran; [4]Department of Radiation Oncology SK Institute of Medical Sciences, Soura Srinagar 190011, India; [5]Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD 20852, USA and [6]International Prevention Research Institute, Lyon 69006, France

Background: Several studies have suggested an association between poor oral health and esophageal squamous cell carcinoma (ESCC). We conducted a case-control study in Kashmir, a region with relatively high incidence of ESCC in north India, to investigate the association between oral hygiene and ESCC risk.

Methods: We recruited 703 histologically confirmed ESCC cases, and 1664 controls individually matched to the cases for age, sex, and district of residence. Conditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: We found an inverse association between teeth cleaning and ESCC risk. As compared with never cleaning teeth, the OR (95% CI) was 0.41 (0.28–0.62) for cleaning less than daily and 0.44 (0.25–0.77) for cleaning at least once a day (P for trend = 0.026) in models adjusted for multiple potential confounders, including several indicators of socioeconomic status. This association persisted after we limited our analyses to never tobacco users. The inverse association between cleaning teeth and ESCC was stronger with using brushes than with using sticks/fingers. We also found an association between the number of decayed, filled, and missing teeth and ESCC risk, but the trend of the associations was not statistically significant. Avoiding solid food and cold beverages because of teeth and oral problems were also associated with ESCC risk.

Conclusion: We found an association between poor oral hygiene indicators and ESCC risk, supporting the previous studies that showed the same associations.

Tobacco smoking and heavy alcohol consumption are major risk factors of esophageal squamous cell carcinoma (ESCC) in Western countries (Kamangar *et al*, 2009). However, in areas with high incidence of ESCC, including central China and northern Iran, these habits are not major risk factors, as many cases of ESCC occur in never smokers and never drinkers (Islami *et al*, 2004; Tran *et al*, 2005). Although several risk factors have been suggested, the major factors contributing to ESCC in those high-incidence areas are yet to be established (Kamangar *et al*, 2009). An association between indicators of poor oral hygiene and ESCC has been reported in several studies from very high-risk areas of China (Abnet *et al*, 2001, 2005b) and Iran (Sepehr *et al*, 2005; Abnet *et al*, 2008b), and from other areas including Latin America, Europe, and Japan (Guha *et al*, 2007; Hiraki *et al*, 2008). However, a few studies have not supported this association (Abnet *et al*, 2005a; Michaud *et al*, 2008).

ESCC is the most common cancer in Kashmir Valley in India (Khuroo *et al*, 1992), where similar to other high-incidence areas, little is known about the etiology of ESCC. We aimed to investigate the association between poor oral hygiene and ESCC risk in the overall population and in never tobacco users in Kashmir.

*Correspondence: Dr NA Dar; E-mail: nazirramzan@gmail.com

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MATERIALS AND METHODS

Subject selection. All cancer cases were recruited at the Regional Cancer Centre and Department of Radiation Oncology of Sher-i-Kashmir Institute of Medical Sciences (SKIMS) from September 2008 to January 2012. Every case in the study was histopatologically confirmed as ESCC and had no previous cancer.

For each case subject, at least one control individually matched to the case for sex and age (± 5 years), and district of residence was recruited from in-patient wards of SKIMS, the Government Medical College Hospital, Srinagar, and 10 district hospitals. Patients were enrolled as controls only when the disease for which they had been admitted did not have a strong association with tobacco or alcohol consumption. The participation rate for cases and control was 96 and 98%, respectively. Other information about the study design and major reasons for hospitalizations of the enrolled controls are provided in detail elsewhere (Dar *et al*, 2012). This study was reviewed and approved by the Institutional Ethics Committee of SKIMS.

Data collection. Structured questionnaires were administered in face-to-face interviews at hospitals by trained interviewers who were able to speak in participants' primary language. A limited number of staff conducted the interviews and no proxies were used. Detailed information on demographic characteristics, habits, including lifelong history of use of alcohol and several tobacco products, and intake of fresh fruits and vegetables, was collected. Ever use of alcohol and tobacco products was defined as the use of the respective product at least weekly for a period of 6 months or more. To assess the socioeconomic status (SES), we built a composite score for wealth, based on appliances ownership and other variables by using multiple correspondence analysis (Islami *et al*, 2009). This score had shown some association with ESCC risk in this population independent of education level (Dar *et al*, 2013). The detailed information about consumption of the various fruits and vegetables was collected using a semi-quantitative food frequency questionnaire. We asked about the usual frequency of use in a day, week, or month and the amount of use in each instance. Using this information, we calculated the intake of each fruit and vegetable in grams per day. In order to cover the intake of seasonal fruits/vegetables, we also collected data on the number of months in which any of these food items had been consumed: the daily intake in these cases was multiplied by the number of months of consumption and divided by 12. The daily intake of all fruits and vegetables were summed up to estimate the total fruit/vegetable intake per day.

The study interviewers, who had been trained by dentists to conduct oral cavity examinations, counted each patient's teeth, recorded number of decayed, missing or filled teeth (the sum of which was DMFT score), and obtained information on teeth brushing habits and the type of instrument used to clean the teeth. Many people in Kashmir do not use modern oral care products. The use of teeth cleaning sticks and twigs (such as willow twigs) and rubbing teeth with charcoal and ash (Dandas) with the fingers is still more common than using brushes and prepared dentifrices (Kaur, 2009; D'Cruz and Aradhya, 2012). In addition, information about the type of foods avoided because of tooth or oral problems was collected.

Statistical analysis. In categorizing the continuous variables, we attempted to have equal number of controls in each category of respective variables. Fruit and vegetable intake data (grams per day) were transformed to logarithmic values following addition of 0.1 to original values. Conditional logistic regression was used to calculate unadjusted and adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). All statistical analysis was done using Stata software, version 11 (Stata Corp., College Station, TX, USA). Two-sided $P<0.05$ were considered statistically significant.

RESULTS

A total of 703 ESCC cases and 1664 matched controls were recruited in this study. Distributions of demographic factors, fruit and vegetable intake, and tobacco and alcohol use by case status are shown in Table 1.

Table 1. Characteristics of 703 ESCC cases and 1664 controls from Kashmir Valley, India, 2008–2012[a]

Characteristics	Cases (%)	Controls (%)	P-value
Age, mean (s.d.), years	61.6 (11.1)	59.8 (11.1)	<0.001
Sex			0.78
Men	393 (55.9)	920 (55.3)	
Women	310 (44.1)	744 (44.7)	
Ethnicity			0.58
Kashmiri	682 (97.0)	1619 (97.3)	
Gojri	11 (1.6)	16 (1.0)	
Pahari	9 (1.3)	27 (1.6)	
Other	1 (0.1)	2 (0.1)	
Place of residence			<0.001
Urban	29 (4.1)	146 (8.8)	
Rural	674 (95.9)	1518 (91.2)	
Education			<0.001
No school	626 (89.0)	1074 (64.5)	
Primary (<5th)	33 (4.7)	203 (12.2)	
Middle (5th–8th)	24 (3.4)	123 (7.4)	
High school (9th–12th)	16 (2.3)	149 (8.9)	
Graduates and higher	4 (0.6)	115 (7.0)	
Wealth score			<0.001
Quintile 1 (lowest)	397 (56.5)	337 (20.2)	
Quintile 2	112 (15.9)	328 (19.7)	
Quintile 3	66 (9.4)	334 (20.1)	
Quintile 4	70 (10.0)	333 (20.0)	
Quintile 5	58 (8.2)	332 (20.0)	
Fresh fruit and vegetable intake, median g per day (inter-quartile range)	7.9 (3.82–12.6)	25.2 (12.0–61.0)	<0.001
Hookah smoking (hookah-years)			<0.001
Never	278 (39.5)	968 (58.2)	
1–139	98 (13.9)	227 (13.7)	
140–240	113 (16.0)	242 (14.6)	
>240	214 (30.4)	225 (13.5)	
Cigarette smoking (pack-years)			0.094
Never	633 (90.0)	1437 (86.3)	
1–6.2	23 (3.2)	78 (4.7)	
6.3–13.1	21 (3.0)	73 (4.4)	
⩾ 13.2	26 (3.7)	76 (4.6)	
Bidi ever smoking	15 (2.1)	3 (0.2)	<0.001
Nass chewing (nass-years)			<0.001
Never	501 (71.5)	1471 (88.5)	
1–119	46 (5.6)	53 (3.2)	
120–199	37 (5.2)	70 (4.2)	
⩾200	117 (16.7)	69 (4.1)	
Gutka ever chewing	10 (1.4)	13 (0.8)	0.01
Alcohol ever use	8 (1.1)	0 (0.0)	<0.001

Abbreviation: ESCC = esophageal squamous cell carcinoma.
[a]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. Numbers may not add up to the total numbers due to missing data in some variables. *P*-values calculated using χ^2-tests for categorical variables (χ^2 for trend in variables with more than two categories) and the Wilcoxon Rank Sum tests for continuous variables.

Approximately 25% of controls cleaned their teeth at least once a day, whereas 6% never cleaned their teeth (Table 2). The frequency of teeth cleaning was inversely associated with ESCC risk. As compared with never cleaning teeth, the OR (95% CI) was 0.41 (0.28–0.62) for cleaning less than daily and 0.44 (0.25–0.77) for cleaning at least once a day (*P* for trend = 0.026). Cleaning teeth with brushes (OR = 0.11; 95% CI: 0.06–0.20) and stick and fingers (OR = 0.51; 95% CI: 0.34–0.77) both were associated with lower ESCC risk. On the other hand, avoiding hard solid foods and cold beverages because of teeth and oral cavity problems were associated with higher ESCC risk. The loss of adult teeth was associated with ESCC risk in unadjusted models, but not in adjusted models. Compared with the referent groups, some categories of the number of decayed, missing, and filled teeth and of DMFT criteria were associated with ESCC risk. However, there was no monotonic trend for the association across increasing categories of exposure.

In never users of any type of tobacco (never smokers and never chewers), the magnitude of the associations between tooth

Table 2. ORs (95% CIs) for the association of high ESCC risk with oral health variables in Kashmiri population

Variables	Cases (%)	Controls (%)	Unadjusted OR (95% CI)	Adjusted OR 1 (95% CI)[a]	Adjusted OR 2 (95% CI)[b]
Frequency of cleaning teeth					
Never	161 (23.0)	101 (6.2)	Referent	Referent	—
Less than daily	460 (65.5)	1130 (69.1)	0.25 (0.19–0.34)	0.41 (0.28–0.62)	—
Daily at least once	81 (11.5)	405 (24.7)	0.11 (0.07–0.16)	0.44 (0.25–0.77)	—
P for trend			<0.001	0.026	—
Instrument used to cleaning teeth					
Do not clean teeth	161 (23.0)	101 (6.2)	Referent	Referent	—
Brush	50 (7.2)	528 (33.3)	0.05 (0.03–0.07)	0.11 (0.06–0.20)	—
Stick or finger	488 (69.8)	957 (60.3)	0.31 (0.23–0.42)	0.51 (0.34–0.77)	—
Avoiding food because of tooth problem					
No problem and no food avoided	523 (78.9)	1426 (89.1)	Referent	Referent	—
Hard solid foods or cold beverages	140 (21.1)	175 (10.9)	2.06 (1.59–2.66)	2.38 (1.64–3.45)	—
Adult tooth loss					
No	108 (15.3)	417 (25.0)	Referent	Referent	—
Yes	595 (84.7)	1247 (75.0)	1.96 (1.52–2.51)	1.31 (0.92–1.87)	—
Number of decayed teeth, median (IQR)	3 (2–4)	2 (1–4)			
Category 1 (0–1)	107 (15.2)	419 (28.8)	Referent	Referent	Referent
Category 2 (2)	204 (29.1)	427 (29.4)	1.98 (1.49–2.63)	2.73 (1.83–4.06)	2.64 (1.79–4.06)
Category 3 (3–4)	271 (38.7)	338 (23.2)	3.26 (2.46–4.33)	3.30 (2.21–4.90)	3.11 (2.07–4.68)
Category 4 (⩾5)	119 (17.0)	271 (18.6)	1.90 (1.37–2.62)	1.47 (0.93–2.32)	1.52 (0.95–2.62)
P for trend			<0.001	0.013	0.014
Number of missing teeth, median (IQR)	3 (1–6)	2 (0–5)			
Category 1 (0)	116 (16.5)	417 (28.7)	Referent	Referent	Referent
Category 2 (1–2)	211 (30.1)	368 (25.3)	1.96 (1.48–2.60)	1.39 (0.92–2.09)	1.29 (0.84–1.98)
Category 3 (3–5)	194 (27.7)	344 (23.6)	2.13 (1.60–2.84)	1.51 (1.00–2.30)	1.36 (0.88–2.11)
Category 4 (⩾6)	180 (25.7)	326 (22.4)	1.96 (1.45–2.66)	0.91 (0.59–1.39)	1.08 (0.68–1.69)
P for trend			<0.001	0.523	0.833
Number of filled teeth, median (IQR)	0 (0–0)	0 (0–0)			
Category 1 (0)	634 (90.6)	1313 (90.2)	Referent	Referent	Referent
Category 2 (1)	17 (2.4)	86 (5.9)	0.46 (0.26–0.80)	0.51 (0.25–1.01)	0.48 (0.29–1.01)
Category 3 (⩾2)	49 (7.0)	56 (3.9)	1.64 (1.10–2.47)	2.08 (1.11–3.89)	1.96 (1.00–3.85)
P for trend			0.256	0.198	0.336
DMFT[c] criteria, median (IQR)	6 (4–10)	5 (3–9)			
Category 1 (0–2)	75 (10.9)	338 (23.7)	Referent	Referent	—
Category 2 (3–4)	136 (19.7)	281 (19.7)	2.34 (1.66–3.31)	2.44 (1.47–4.03)	—
Category 3 (5–6)	159 (23.1)	271 (19.0)	2.62 (1.86–3.69)	1.85 (1.14–3.00)	—
Category 4 (7–10)	157 (22.8)	276 (19.3)	2.92 (2.07–4.12)	1.93 (1.19–3.13)	—
Category 5 (⩾11)	162 (23.5)	261 (18.3)	3.07 (2.15–4.37)	1.54 (0.93–2.54)	—
P for trend			<0.001	0.449	—

Abbreviations: CI = confidence intervals; ESCC = esophageal squamous cell carcinoma; IQR = inter-quartile range; OR = odds ratio. Numbers may not add up to the total numbers due to missing data in some variables.

[a]Adjusted for age, ethnicity, residence, education, wealth score, fruit and vegetable intake, bidi smoking, gutka chewing, alcohol consumption and cumulative use of hookah, cigarette, and nass.

[b]ORs (95% CIs) for decayed, missing, and filled teeth were mutually adjusted for each other in addition to adjustments for above covariates.

[c]DMFT is the number of decayed, missing, or filled teeth.

variables other than the number of decayed teeth and of the inverse association between teeth cleaning frequency and ESCC risk were slightly strengthened (Table 3). The above associations were slightly stronger in never tobacco smokers (Supplementary Table 1) than in never tobacco chewers (Supplementary Table 2).

In analyses stratified by the wealth score, the inverse association between frequency of cleaning teeth and ESCC risk and the association between DMFT criteria and ESCC risk was stronger in people with higher wealth score than those with lower score (Supplementary Table 3). The other associations in the subgroups were similar to the overall associations.

DISCUSSION

Our study showed an inverse association between teeth cleaning and ESCC risk in the Kashmir Valley in the overall study and in

Table 3. ORs (95% CIs) for the association between oral health indicators and ESCC risk in never tobacco smokers (hookah, cigarette, and bidi) and chewers (nass and gutka)

Variables	Cases (%)	Controls (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Frequency of cleaning teeth				
Never	52 (27.4)	32 (4.3)	Referent	Referent
Less than daily	106 (55.8)	457 (61.4)	0.19 (0.09–0.40)	0.25 (0.09–0.71)
Daily at least once	32 (16.8)	255 (34.3)	0.09 (0.04–0.22)	0.34 (0.09–1.21)
P for trend			<0.001	0.392
Instrument used to cleaning teeth				
Do not clean teeth	52 (27.4)	32 (4.5)	Referent	Referent
Brush	20 (10.5)	296 (41.2)	0.05 (0.02–0.13)	0.10 (0.03–0.39)
Stick or finger	118 (62.1)	390 (54.3)	0.26 (0.12–0.56)	0.34 (0.12–0.96)
Avoiding food because of tooth problem				
No problem and no food avoided	145 (81.0)	666 (90.1)	Referent	Referent
Hard solid or cold beverages	34 (19.0)	73 (9.9)	2.67 (1.42–5.03)	4.32 (1.54–12.09)
Adult tooth loss				
No	31 (16.2)	243 (31.8)	Referent	Referent
Yes	160 (83.8)	522(68.2)	3.14 (1.81–5.44)	2.29 (1.06–4.95)
Number of decayed teeth				
Category 1 (0–1)	38 (20.1)	203 (30.4)	Referent	Referent
Category 2 (2)	61 (32.3)	212 (31.8)	1.51 (0.85–2.67)	2.10 (0.86–5.14)
Category 3 (3–4)	60 (31.7)	151 (22.6)	1.89 (1.05–3.39)	2.91 (1.18–7.16)
Category 4 (⩾5)	30 (15.9)	101 (15.2)	1.04 (0.53–2.04)	0.65 (0.23–1.83)
P for trend			0.500	0.970
Number of missing teeth				
Category 1 (0)	33 (17.5)	242 (36.4)	Referent	Referent
Category 2 (1–2)	54 (28.5)	170 (25.5)	3.11 (1.64–5.90)	2.75 (1.09–6.90)
Category 3 (3–5)	57 (30.2)	137 (20.5)	3.88 (2.00–7.51)	2.23 (0.84–5.97)
Category 4 (⩾6)	45 (23.8)	117 (17.6)	3.37 (1.61–7.02)	2.10 (0.76–5.81)
P for trend			<0.001	0.171
Number of filled teeth				
Category 1 (0)	173 (92.0)	608 (91.2)	Referent	Referent
Category 2 (1)	3 (1.6)	35(5.2)	0.35 (0.09–1.25)	0.29 (0.05–1.78)
Category 3 (⩾2)	12 (6.4)	24 (3.6)	1.86 (0.69–4.94)	2.64 (0.49–14.34)
P for trend			0.654	0.693
DMFT[b] criteria				
Category 1 (0–2)	26 (13.9)	188 (28.7)	Referent	Referent
Category 2 (3–4)	32 (17.1)	154 (23.5)	2.34 (1.07–5.15)	3.16 (1.02–9.82)
Category 3 (5–6)	48 (25.7)	110 (16.8)	4.90 (2.17–11.04)	2.92 (0.89–9.60)
Category 4 (7–10)	40 (21.4)	112 (17.1)	3.13 (1.49–6.61)	2.64 (0.94–7.41)
Category 5 (⩾11)	41(21.9)	91 (13.9)	4.12 (1.78–9.56)	2.15 (0.65–6.84)
P for trend			<0.001	0.244

Abbreviations: CI = confidence intervals; ESCC = esophageal squamous cell carcinoma; OR = odds ratio. Numbers may not add up to the total numbers due to missing data in some variables.
[a]Adjusted for age, ethnicity, residence, education, wealth score, fruit and vegetable intake, and alcohol consumption.
[b]DMFT is the number of decayed, missing, or filled teeth.

never tobacco users. We also found associations between risk of ESCC and several other indicators of poor oral hygiene.

Our results are in agreement with several other studies (Abnet *et al*, 2001; Sepehr *et al*, 2005; Wei *et al*, 2005; Abnet *et al*, 2008a, b). Poor oral hygiene can lead to periodontal disease. Periodontal disease and caries both are characterized by chronic bacterial infections, the major causes of tooth damage and loss in adults (Thomas *et al*, 1994; Papapanou, 1996; Shigli *et al*, 2009). Tobacco smoking, a risk factor for ESCC, can also cause periodontal disease and tooth loss (Pihlstrom *et al*, 2005). In addition, low SES, which may be associated with poor oral health, has consistently been linked to ESCC risk (Islami *et al*, 2009). Therefore, the association between poor oral hygiene and ESCC can be confounded by tobacco use and SES. However, the association between oral hygiene indicators persisted in our study after excluding tobacco users from the analysis. The majority of these associations also persisted in analyses stratified by a composite score for wealth, suggesting that confounding by SES does not explain these findings.

Mechanistic pathways linking oral hygiene and ESCC are currently unknown. Individuals with missing teeth may have a different burden of oral flora and may have communities that more effectively reduce nitrate to nitrite (Eisenbrand *et al*, 1980), a necessary step in the *in-vivo* formation of nitrosamines (Nair *et al*, 1996). This endogenous formation accounts for 45–75% of a typical individual's nitrosamine exposure (Tricker, 1997). Studies have also shown that oral bacteria that cause periodontal diseases can convert ethanol or dietary sugars into acetaldehyde, a carcinogenic metabolite of ethanol (Salaspuro, 2003a, b). In addition, a periodontal infection can lead to a release of inflammatory mediators (proinflammatory cytokines) (Scannapieco, 2004). The host response to bacterial inflammation are known to have a role in development of cancer (Karin *et al*, 2006). However, although a meta-analysis of one prospective and six case-control studies have suggested an inverse association between the use of nonsteroidal anti-inflammatory drugs and esophageal cancer (Sun and Yu, 2011), the role of chronic inflammation in ESCC is less clear.

Histological ascertainment of ESCC diagnosis, collection of extensive information on potential confounders, and large sample size were among the strengths of this study. One of the main limitations was that oral examinations were done by interviewers who were not dental care professionals. However, it is unlikely to have major influence on the reported number of missing and filled teeth or in the accurate reporting of oral hygiene practices. Because of retrospective assessments of exposure, information bias might have been existed in assessment of some variables of interest and covariates. However, information bias with teeth counting is unlikely. Finally, although we adjusted our results for multiple potential confounding factors, existence of some unknown confounders in this population or residual confounding could not totally be excluded. Nevertheless, consistency of our main finding in our several sub-analyses and with studies in other population suggests that the association is real.

In summary, this study showed associations between several indicators of poor oral hygiene and ESCC risk, which support the results of the previous studies in several other populations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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