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Missing and decayed teeth, oral hygiene and dental staining in relation to esophageal cancer risk: ESCCAPE case-control study in Kilimanjaro, Tanzania

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Abstract

In the African esophageal squamous cell carcinoma (ESCC) corridor, recent work from Kenya found increased ESCC risk associated with poor oral health, including an ill-understood association with dental fluorosis. We examined these associations in a Tanzanian study, which included examination of potential biases influencing the latter association. This age and sex frequency-matched case-control study included 310 ESCC cases and 313 hospital visitor/patient controls. Exposures included self-reported oral hygiene and nondental observer assessed decayed+missing+filled tooth count (DMFT index) and the Thylstrup-Fejerskov dental fluorosis index (TFI). Blind to this nondental observer TFI, a dentist independently assessed fluorosis on photographs of 75 participants. Odds ratios (ORs) are adjusted for demographic factors, alcohol and tobacco. ESCC risk was associated with using a chewed stick to brush teeth (OR 2.3 [95% CI: 1.3-4.1]), using charcoal to whiten teeth (OR 2.13 [95% CI: 1.3, 4.1]) and linearly with the DMFT index (OR 3.3 95% CI: [1.8, 6.0] for ≥10 vs 0). Nondental observer-assessed fluorosis was strongly associated with ESCC risk (OR 13.5 [95% CI: 5.7-31.9] for TFI 5+ v 0). However, the professional dentist's assessment indicated that only 43% (10/23) of participants assessed as TFI 5+ actually had fluorosis. In summary, using oral charcoal, brushing with a chewed stick and missing/decayed teeth may be risk factors for ESCC in Tanzania, for which dose-response and mechanistic research is needed. Links of ESCC with "dental fluorosis" suffered from severe exposure misclassification, rendering it impossible to disentangle any effects of fluorosis, extrinsic staining or reverse causality.

Abbreviations: DMFT, DMFT index is the sum of decayed, missing and filled teeth; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; ESCCAPE, Esophageal Squamous Cell Cancer African PrEvention research; OR, odds ratio; RA, research assistant; TFI, Thlystrup-Fejerskov index of dental fluorosis.

KEYWORDS
esophageal cancer, fluorosis, oral health, Tanzania

1 | INTRODUCTION

Esophageal cancer (EC), predominantly esophageal squamous cell carcinoma (ESCC), is the third most common cause of cancer death in Eastern Africa.[1] The hypothesized etiological model for this African EC corridor involves the presence of unknown spatially patterned factors conveying substantial risk on top of which lifestyle factors act.[2] Established and strongly suggested risk factors for ESCC (in any setting) include tobacco, alcohol, low fruit and vegetable intake, opium use, polycyclic aromatic hydrocarbons, micronutrient deficiencies, hot beverages and poor oral health, although the role of mycotoxins and infections including HIV is uncertain.[2,3] For each of these factors, we recently reviewed exposure sources, prevalence and relationship to ESCC risk in Africa and found that each of them, except opium, may contribute to Africa's ESCC burden. However, the evidence base for ESCC in Africa is relatively thin and not entirely consistent.[2] Since then, alcohol and hot beverages have been identified as risk factors in Kenya.[4,5]

Tanzania lies within the African EC corridor with an estimated 2500 new cases in 2018 and the same number of deaths.[1] Although fine-scale data on spatial variations in incidence across the country are few, there are suggestions of higher incidence in the coastal zone and in the northern regions of Tanga and Kilimanjaro. This EC burden was documented by Hiza as early as in 1976[6] and appears to persist today.[7] Men have higher incidence rates than women and like in other African settings, the disease also occurs in young people.[7]

ESCC etiological and clinical research is now underway across East Africa within the African EC Consortium (AfrECC).[8] The etiological research includes the ESCC African PrEvention research (ESCCAPE) case-control studies, which were conducted in Kenya,[9] Malawi and the subject of the present analysis, Tanzania. Oral health is among the ESCC risk factors being investigated in ESCCAPE because in every high-incidence ESCC population worldwide, certain features of poor oral health have been implicated in ESCC. Notably, studies in Asia,[10-15] the United States,[16] Kenya[17,18] and a European-Latin American study[19] reported positive associations of ESCC with at least one of the following oral diseases or conditions: chronic periodontal diseases, poor oral hygiene, dental decay and, as illustrated in Chen et al.'s meta-analysis, tooth loss.[20] The magnitude of increased ESCC risk was of the order of 1.2-fold for oral leucoplakia,[15] 1.5- to 2.5-fold for extremes of missing teeth, and 2- to 3-fold for lack of daily tooth brushing. Among these studies, in 2019, the Kenyan ESCCAPE case-control study found strong associations with the number of decayed teeth, and moderate associations with the number of missing teeth and indicators of poor oral hygiene, namely lack of daily tooth brushing and brushing with a chewed branch stick.[18] Additionally, among participants with at least four decayed/missing teeth, the Kenyan study reported on an association of ESCC with the presence of dental fluorosis.[18] This attribute was visually assessed by trained fieldworkers who were not dental professionals, but dentition photographs were not taken for exposure validation. In the East African setting, excessive fluoride exposures in early life typically manifest as brown stains and pitting of the hypomineralized enamel of permanent dentition. The association of ESCC with dental fluorosis in Kenya raised intrigue because the African ESCC corridor is closely colocated with the African fluoride belt.[18] However, to our knowledge, there is no evidence of carcinogenicity of fluoride. Inorganic fluoride in drinking water was reviewed by the International Agency for Research on Cancer (IARC) monograph programme as not classifiable as to its carcinogenicity to humans (Group 3).[21] Furthermore, other settings formerly affected by dental fluorosis such as Colorado in the United States, where it was first known as the "Colorado brown stain,"[22] have not been documented as having raised ESCC incidence.

> **What's new?**
> The putative etiological model for the African oesophageal cancer corridor involves a combination of unknown spatially-patterned factors and lifestyle factors such as poor oral health. The association of oesophageal cancer with dental fluorosis in Kenya, in addition to expected associations with dental decay/loss, recently raised intrigue. In the present Tanzanian case-control study, findings were consistent with those from Kenya. However, a review of oral photographs indicated serious fluorosis exposure misclassification, rendering it impossible to disentangle any effects of fluorosis, extrinsic staining, or reverse causality.

Prompted by these Kenyan observations, upon recent completion of recruitment in the second ESCCAPE case-control study location in Northern Tanzania, and thus contributing to assessing "consistency" among the Bradford-Hill guidelines for causality,[23] we prioritized analysis of oral health in relation to ESCC in Tanzania. In this setting, like in parts of Kenya's Rift Valley and highland areas, there are localized areas of naturally occuring high fluoride in the Kilimanjaro, Arusha-Meru and Manyara regions. Fluoride exposures to the population originate from consumption of ground and surface water, trona (*magadi*) and tea.[24] Subsequent to the Kenyan findings, during the later phase of fieldwork in Tanzania, we also obtained a mobile phone photograph of the participant's dentition, which allowed for a crude assessment of whether the dental staining observed was due to dental fluorosis. Herein, we present the findings for missing and decayed teeth, oral hygiene practices and dentition staining in relation to ESCC in northern Tanzania.

2 | METHODS

2.1 | Study setting

We conducted a hospital-based case-control study of esophageal cancer in Northern Tanzania. The participating hospitals were all located in the Kilimanjaro region (Supplementary Figure 1). Recruitment was primarily conducted at the Kilimanjaro Christian Medical Center (KCMC) located in Kilimanjaro's capital Moshi. KCMC operates a daily endoscopy clinic to which patients from across the Kilimanjaro region and beyond are referred. Study interviewers were based at KCMC. The other participating hospitals were Huruma Hospital in Rombo, Hai and Siha District Hospitals, Kibosho hospital and the Machame Lutheran Hospital. These peripheral hospitals are located up to 70 km from KCMC. They do not have functioning endoscopy facilities and Huruma Hospital alone conducts barium swallow. Investigators at each of these hospitals participated in the ESCCAPE study and when they referred suspected EC patients to KCMC, they liaised with the study interviewers. Additionally, because many patients were too weak to travel to KCMC, the study interviewers traveled to the peripheral hospitals at least once per month to interview their EC patients.

2.2 | Eligibility criteria

The case inclusion criteria were patients newly diagnosed at age ≥ 18 years with esophageal squamous cell cancer in the Kilimanjaro region of Tanzania. Cases were included based on histological confirmation of ESCC, diagnosis via imaging (barium swallow) or via clinical presentation with solid and/or liquid dysphagia and severe weight loss. Inclusion of nonhistologically confirmed cases is justified in this setting as these aforementioned symptoms are very specific because diagnosis is very late. Notably, in a Malawian study of endoscopy and histology-confirmed EC tumors, 86% were obstructive,[25] and thus cause dysphagia and wasting. Furthermore, over 90% of esophageal cancer in East Africa is ESCC,[26] thus clinically diagnosed cases do not add major outcome misclassification.

Controls were over 18 years of age at recruitment and did not have cancer or any other digestive disease. They were recruited from the same hospitals as cases, from in-patients, out-patients and hospital visitors. Controls were recruited in a 1:1 ratio to cases, using age and sex frequency matching to the cases' distribution.

2.3 | Participant recruitment

Recruitment occurred continuously between November 2015 and December 2019. All confirmed/suspected cases presenting at the participating hospitals were invited to participate. Of a total of 345 potential cases approached, 322 (93%) agreed to participate (Supplementary Figure 2). Twelve of these cases (6%) were later excluded from the study as their histology revealed adenocarcinoma (n = 10), one neuroendocrine tumor and one other malignancy. The remaining 310 cases were included in the present analyses of which 79% (N = 244) were recruited at KCMC, and the remaining 21% of cases (N = 66) were recruited at the peripheral hospitals. Of the 244 cases recruited at KCMC, 198 had a histological confirmation of ESCC, 30 were endoscopy-confirmed without pathology, 11 clinically and 5 through imaging. Most (86%) of the cases recruited at the peripheral hospitals were clinically diagnosed. Note that some patients recruited at KCMC did not undergo endoscopy, despite the service being available, because they were too weak or ill to undergo this uncomfortable procedure.

To achieve the frequency matching of controls to the age and sex distribution in cases, in the first year of recruitment we generated an age-sex target distribution based on that for previously diagnosed KCMC ESCC patients and from the second year onwards, the targets were updated annually based on the study's actual age-sex distribution of cases. The controls were outpatients (17%), inpatients (7%) and hospital visitors (76%) who were approached in an ad hoc fashion in the hospital grounds. A high proportion of controls agreed to participate (99%).

A sample size of at least 290 cases and 290 controls was aimed for, which provided 80% power at a 5% false-positive percentage to detect odds ratios of 1.6 or larger for a dichotomous control exposure prevalence of 50% in controls. We recruited a 5% excess beyond this target to allow for inevitable exclusions.

2.4 | Data and specimen collection

The study included a face-to-face questionnaire on lifestyle and sociodemographic factors, with all data collected in real time on mobile phones using a specially programmed mHealth ESCCAPE study application hosted by Mobenzi. This was administered by the study research assistants (RAs) who also collected an Oragene saliva sample from all participants. In addition, participants recruited at the central site KCMC, where laboratory facilities were available, were asked to provide two 5 mL blood samples, a 25 mL urine sample and agreement to additional tumor biopsy specimen being taken at endoscopy in the case group only. Participants who completed the questionnaire but did not provide bio-specimen were included in the study and in the present analysis.

2.5 | Oral health

As part of the questionnaire, participants were asked about oral hygiene practices. Questions in this section were about the frequency of oral hygiene/tooth brushing, collected in the categories: daily, 4 to 6 times/week, 1 to 3 times/week, less than once/week and never. We asked about whether the brushing implement was a plastic toothbrush, wood/chewed branch tip/stick or other. Participants were also asked if they had ever used charcoal ("*mkaa*" in kiswahili) to clean/whiten teeth. Responses were obtained as "never use," "daily use" and "less than daily use." Additionally, the RA, a nondental observer, assessed hard tissue of the oral cavity as follows. The number of decayed (D), missing (M) and filled teeth (FT) were counted and their sum generated the DMFT index, which ranges from 0 DMFT as the best to 32 DMFT as the worst.[27] For dentate participants, dental fluorosis was assessed using the Thylstrup-Fejerskov index (TFI).[28] Its scores range from TFI 0 for no dental fluorosis to TFI 9 for very severe fluorosis with extensive loss of the enamel and changes of the anatomical surface of a tooth. For this assessment, RAs were provided with the illustrative guide in Supplementary Figure 3.

This oral health assessment protocol was followed for the first 3 years of recruitment. In the fourth year, from 12 January 2019 onwards and upon approval of a protocol amendment and agreement of each participant, an oral photograph was additionally taken for all cases and controls who agreed. A photograph of the front incisors was taken using a mobile phone, with anonymity of the participant strictly observed. These photographs were independently reviewed by a professional dentist (DSR) who was blind to the case-control status and to the TFI score originally assessed by the nondental RA. This expert rating allowed for an assessment of exposure misclassification of fluorosis as assessed by the nondental observer. Fluorosis can be prone to misclassification by an untrained nondental professional if extrinsic dental staining not due to fluorosis is mistaken as fluorosis.

2.6 | Other exposure variables

For the present investigation, socioeconomic factors such as job, education and amenities, age, being of the majority Chagga ethnicity or not, alcohol consumption (current/past/never), tobacco use (smoking and smokeless), hot beverage consumption, household air pollution and family history of esophageal cancer in parents or siblings represent potential confounders or effect modifiers.

2.7 | Statistical analysis

The analytical strategy followed was to first compare characteristics of cases and controls to assess whether controls represented the population from which cases originated. These crude associations were examined using chi-squared tests with characteristics grouped categorically. Second, we examined correlates of oral hygiene and health in controls, which served to understand the determinants of these exposures of interest and in turn may act as confounders. These associations were investigated by examining differences in the proportion of users of chewed sticks and oral charcoal to clean teeth, differences in the mean number of missing, decayed and DMFT scores (assumed to be Poisson counts) and difference in TFI scores (continuous). For each of these oral health attributes, differences in prevalence/means were examined separately for sex, Chagga ethnicity, resident of Moshi urban, joint ever drinker-ever tobacco users, age (under or over 50 years) and educational level. Being resident of the "Moshi urban" district was a factor of interest because cancer case-control studies conducted in hospital settings in Africa are vulnerable to selection biases due to controls disproportionately residing nearer the recruiting hospital, whereas cancer cases often originate from further afield. This may introduce bias if urban residents differ in their oral health status. In the context of the Kilimanjaro region, this may manifest as differences in the distribution of ethnic groups, thus being from the Chagga tribe, the predominant ethnic group in the Kilimanjaro region, was also examined as a determinant of oral health and as a potential confounder.

Third, we examined associations of the exposures of interest with ESCC using logistic regression models to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). A basic model (Model 1) was first fitted with adjustment for design and demographic factors (OR_1). These factors were gender and age, Chagga ethnicity, education and residential district. In Model 2, OR_2 was further adjusted for two potential lifestyle confounders, alcohol consumption and tobacco use (ie, both smoking and smokeless tobacco). These OR_2 values are quoted in the abstract. Finally, in Model 3, OR_3 values were further mutually controlled for oral hygiene/health indicators: tooth brush type, brushing frequency, DMFT score and nondental observer-assessed TFI. For each model, analyses based on all participants were first conducted. Thereafter, subgroup analyses were performed among never tobacco and never-oral charcoal users to remove confounding by those factors (identified in Step 2). Likewise, analyses were conducted among non-Moshi urban residents due to the excess of controls in that district (identified in Step 1) and stratified by DMFT due to strong effect modification in previous studies. Analyses in never tobacco users included fewer cases than controls due the strong association of tobacco with ESCC, and had a higher proportion of women because of a large sex-differential in tobacco use. Statistical analyses were conducted using Stata version 15.0.

3 | RESULTS

3.1 | Participants' profile

Characteristics of the 310 cases and 313 controls included are shown in Table 1. Mean age at diagnosis was 63.7 years (SD 14) in cases and at interview was 62.4 (14.2) years in controls; 5% of cases were under age 40 and 76% were men. By design, distributions of age and sex were similar in the control group. Over 85% of the participants lived in the Kilimanjaro region. They were predominantly Chagga (70%) people from the districts of Rombo, Hai and Moshi-Rural, followed by the neighboring regions of Arusha, Tanga and Manyara. More controls (9%) than cases (2%) resided in the Moshi Urban district, that is, the district where KCMC is located. Formal education was lower among cases (20% none, 64% some/all primary, 13% secondary or higher) than controls (7% none, 74% some/all primary and 20% secondary or higher) (Table 1). This observation held after exclusion of participants who were residents of the Moshi-Urban district. Both tobacco and alcohol use were more common in cases than controls. There were 3 times as many ever tobacco users in cases than in controls in each sex (in men: 81% in cases vs 24% in controls and in women: 32% in cases vs 11% in controls). Ever alcohol consumption was extremely high in male cases (85%).

3.2 | Dental staining and dental fluorosis

Of 98 participants (63 cases and 35 controls) who were asked if an oral health photograph could be taken, 93 (95%, 59 cases, 34 controls) agreed and their photographs were reviewed for no/possible/definite fluorosis by a professional dentist. No judgment on fluorosis could be made for 16 of 93 (17%) due to no teeth or poor photo quality. Of the remaining 75 photographs evaluated (47 cases, 28 controls), the distribution of dentist-assessed fluorosis by categories of the original nondental observer TFI is shown in Figure 1. There was clearly an increased proportion of dentist-assessed definite fluorosis with higher nondental observed TFI (*P* = .003). In participants that the nondental

TABLE 1 Demographic characteristics and alcohol and tobacco consumption, in cases and controls, ESCCAPE Tanzania case-control study

		310 cases		313 controls		
	Category	N	%	N	%	*P* value[a]
Sex	Male	237	76	237	76	.83
	Female	73	24	76	24	
Age (years) at diagnosis/interview	18 to 29	2	0.7	7	2.2	.58
	30 to 39	12	3.9	13	4.2	
	40 to 49	43	13.9	39	12.5	
	50 to 59	62	20.0	64	20.5	
	60 to 69	95	30.7	86	27.5	
	70+	96	31.0	104	33.2	
	Mean (SD)	63.7	(14.1)	62.4	(14.2)	—
Residential region and Kilimanjaro district	Kilimanjaro—Rombo	76	24.5	88	28.1	<.001
	Kilimanjaro—Hai	61	19.7	70	22.4	
	Kilimanjaro—Moshi rural	61	19.7	68	21.7	
	Kilimanjaro—Mwanga	8	2.6	11	3.5	
	Kilimanjaro—Moshi urban	6	1.9	27	8.6	
	Kilimanjaro—Same	5	1.6	11	3.5	
	Kilimanjaro—Siha	15	4.8	5	1.6	
	Arusha	31	10.0	19	6.1	
	Other[b]	47	15.2	14	4.5	
Formal educational level	None	63	20.3	21	6.7	<.001
	Primary (partial)	89	28.7	69	22.0	
	Primary (completed)	118	38.1	162	51.8	
	Secondary or higher	40	12.9	61	19.5	
Ethnic group[c]	Chagga	200	64.5	230	73.5	.02
	Pare	16	5.2	34	10.9	.01
	Maasai	19	6.1	10	3.2	.08
	Meru	16	5.2	7	2.2	.05
Alcohol use (men) men	Never	35	14.8	124	52.3	<.001
	Ever	202	85.2	113	47.7	
Alcohol use (women)	Never	41	56.2	49	64.5	.30
	Ever	32	43.8	27	35.5	
Tobacco use[d] (men)	Never	44	18.6	180	76.0	<.001
	Ever	193	81.4	57	24.1	
Tobacco use[d] (women)	Never	50	68.5	68	89.5	.002
	Ever	23	31.5	8	10.5	

[a]*P* value from chi-squared test of difference in the categorical distribution between cases and controls.
[b]Other: Tanga, Manyara, Morogoro, Singida, Dodoma regions.
[c]Ethnic group: multiple selections possible thus the chi-squared test is carried out for the association of case-control status with each group. Only the major ethnic groups are presented.
[d]Tobacco use includes both smoking and smokeless tobacco: in male controls, most tobacco use is smoking (91%) alone, 5% smoking and smokeless and 5% smokeless only while in female controls, tobacco use was low and was entirely smokeless use.

observed rated as TFI 0 (no fluorosis), the majority (87% = 13/15) were also considered as "no fluorosis" by the dentist. However, in the group of participants that the nondental observer assessed as TFI 5 or higher, the dentist considered that only 43% (10/23) were definite fluorosis, 26% (6/23) were possible fluorosis and 30% (7/23) were not fluorosis. Examples of the photographs evaluated are shown in Figure 2. Figure 2A is dental fluorosis, whereas Figure 2B-D was "false positives," that is, the stains were rated as degrees of dental fluorosis by the RA but were in fact extrinsic staining due to caries, root decay and developmental disturbances, respectively. Based on this evaluation, all associations with the nondental observer assessed TFI index need to be considered in light of this serious misclassification.

3.3 | Oral health in controls

Almost all controls practiced daily oral hygiene (97%), typically (91%) with a modern toothbrush. A small proportion (9%) used a wood/chewed stick toothbrush (Table 2). Ever oral charcoal use was reported by 11% of controls but only 3% of all controls reported daily use. The

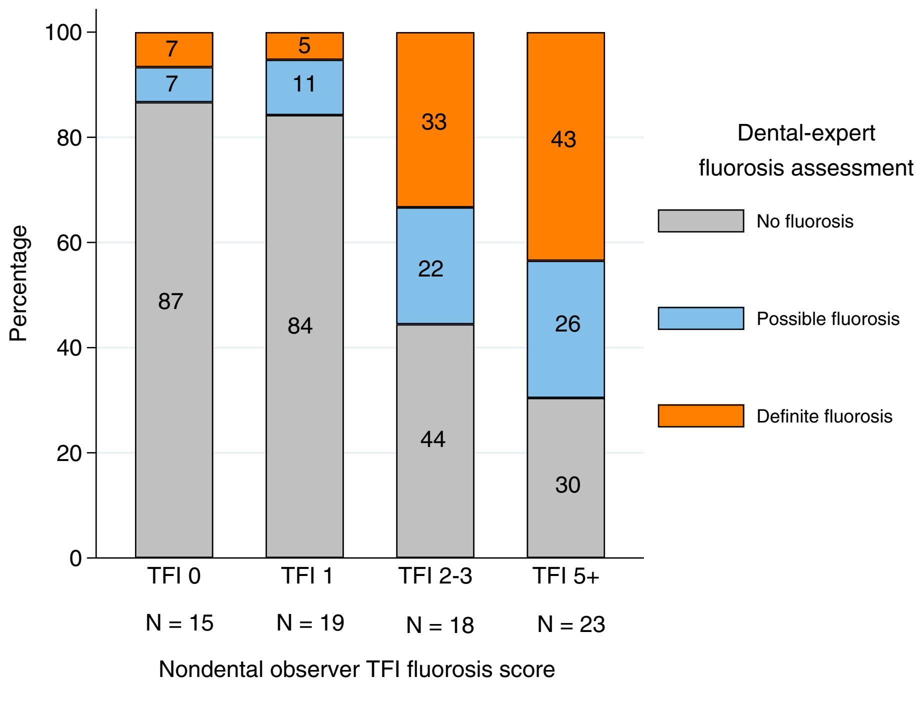

FIGURE 1 Distribution of possible presence of fluorosis assessed on 75 photographs by a professional dentist for categories of Thylstrup-Fejerskov index originally assessed by the study's nondental observer

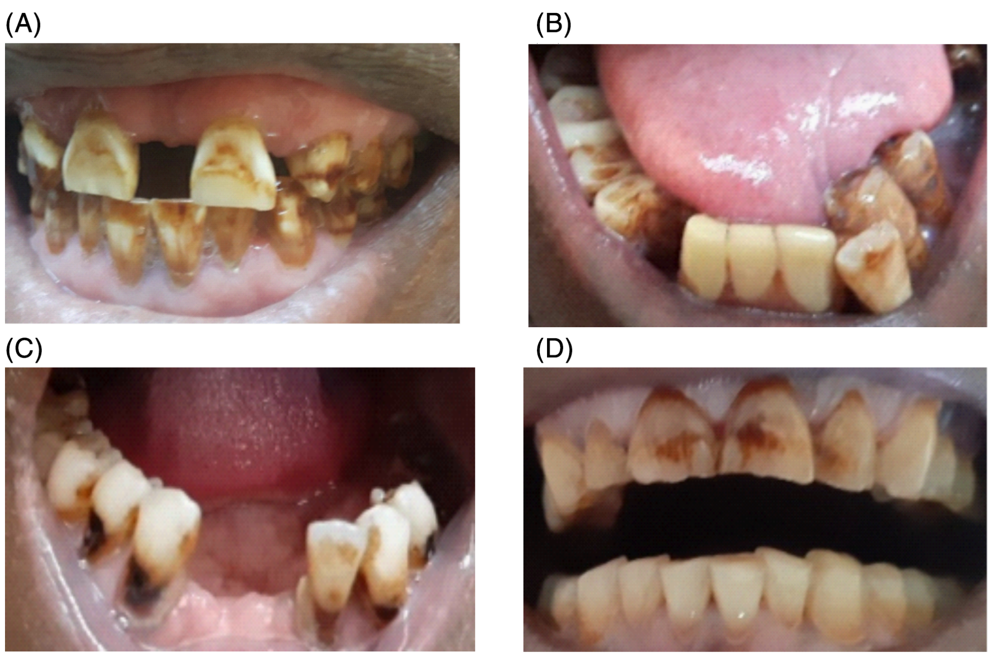

FIGURE 2 Example of oral health photographs considered as (A) Thylstrup-Fejerskov score of 4 + by the nondental observer, in agreement with the professional dentist's evaluation of the presence of fluorosis; (B-D) Thylstrup-Fejerskov score of 5+ by the nondental observer, for which the dentist did not consider as fluorosis but instead were (B) extrinsic staining; (C) stained roots with exposure cementum and (D) development disturbance affecting central incisors

TABLE 2 Distributions of oral health and hygiene attributes in controls, overall and by ESCC risk factors

Characteristic	Category	N[a]	Ever use of oral charcoal Percent (95% CI)	Ever use of chewed stick Percent (95% CI)	No. missing teeth Mean (95% CI)	No. decayed teeth Mean (95% CI)	DMFT score Mean (95% CI)	Staining level: 0 (none) to 9 (high) Mean (95% CI)
	All	313	11 (8, 15)	8 (5, 12)	2.9 (2.7, 3.1)	1.5 (1.4, 1.6)	4.6 (4.4, 4.9)	1.6 (1.4, 1.8)
Sex	Men	237	8 (5, 13)	7 (4, 11)	2.8 (2.6, 3.0)	1.5 (1.4, 1.7)	4.6 (4.3, 4.8)	1.6 (1.4, 1.8)
	Women	76	20 (11, 30)	11 (5, 20)	3.1 (2.7, 3.5)	1.3 (1.1, 1.6)	4.9 (4.4, 5.4)	1.6 (1.2, 2.0)
	P		.007	.50	.20	.13	.23	.99
Age (years)	<50	59	14 (6, 25)	7 (2, 16)	2.1 (1.7, 2.5)	0.8 (0.6, 1.1)	3.0 (2.6, 3.5)	0.7 (0.4, 1.0)
	≥ 50	254	11 (7, 15)	8 (5, 12)	3.1 (2.9, 3.3)	1.6 (1.5, 1.8)	5.0 (4.7, 5.3)	1.8 (1.6, 2.0)
	P		.52	.57	<.001	<.001	<.001	<.001
Alcohol and tobacco (joint ever/never use)	Never alcohol, never tobacco	161	5 (2, 10)	3 (1, 6)	2.7 (2.5, 3.0)	1.4 (1.3, 1.6)	4.6 (4.3, 5.0)	1.3 (1.1, 1.5)
	Ever alcohol, never tobacco	87	17 (10, 27)	7 (3, 14)	2.6 (2.2, 2.9)	1.3 (1.1, 1.5)	4.0 (3.6, 4.4)	1.3 (1.0, 1.6)
	Never alcohol, ever tobacco	10	20 (3, 56)	20 (3, 56)	3.6 (2.5, 5.0)	1.8 (1.1, 2.8)	5.4 (4.1, 7)	2.9 (1.5, 4.3)
	Ever alcohol, ever tobacco	55	18 (9, 31)	24 (13, 37)	3.7 (3.2, 4.2)	1.9 (1.5, 2.3)	5.6 (5.0, 6.2)	2.7 (2.2, 3.3)
	P		.005	<.001	<.001	.05	<.001	<.001
Education	Completed primary or higher	223	9 (6, 14)	4 (2, 8)	1.9 (1.7, 2.1)	1.3 (1.1, 1.4)	3.3 (3, 3.5)	1.3 (1.1, 1.5)
	Did not complete primary	90	17 (10, 26)	19 (12, 29)	5.3 (4.8, 5.8)	2 (1.7, 2.3)	8.0 (7.4, 8.6)	2.4 (2.1, 2.7)
	P		.05	<.001	<.001	<.001	<.001	<.001
Ethnicity	Chagga	230	12 (8, 17)	7 (4, 11)	2.5 (2.3, 2.8)	1.4 (1.3, 1.6)	4.1 (3.9, 4.4)	1.6 (1.4, 1.8)
	Not Chagga	83	10 (4, 18)	12 (6, 21)	3.8 (3.4, 4.3)	1.7 (1.4, 2)	6.0 (5.5, 6.6)	1.5 (1.1, 1.9)
	P		.60	.20	<.001	.15	<.001	.49
Residence	Moshi-urban	27	7 (1, 24)	0 (0, 13)	1.3 (0.9, 1.8)	1.0 (0.7, 1.5)	2.3 (1.7, 2.9)	1.0 (0.5, 1.4)
	Not Moshi-urban	286	12 (8, 16)	9 (6, 13)	3.0 (2.8, 3.3)	1.5 (1.4, 1.7)	4.9 (4.6, 5.1)	1.7 (1.5, 1.8)
	P		.51	.09	<.001	.02	<.001	.04
Brushing	Toothbrush user	285	10 (7, 14)	—	2.5 (2.4, 2.7)	1.5 (1.4, 1.7)	4.3 (4.1, 4.6)	1.4 (1.3, 1.6)
Implement	Chewed stick user	27	26 (11, 46)	—	5.7 (4.8, 6.7)	1.3 (0.9, 1.8)	7.1 (6.1, 8.2)	3.2 (2.3, 4.0)
	P		.01		<.001	.40	<.001	<.001
Oral charcoal use	Never	277	—	7 (4, 11)	2.8 (2.6, 3.0)	1.4 (1.3, 1.6)	4.5 (4.2, 4.7)	1.5 (1.4, 1.7)
	Ever	35	—	17 (7, 34)	3.9 (3.2, 4.6)	1.9 (1.5, 2.5)	5.9 (5.1, 6.7)	1.9 (1.3, 2.5)
	P			.01	<.001	.02	<.001	.18

[a]N = 313 controls applied throughout except for ever use of a chewed stick to brush, where there is one missing value.

TABLE 3 Odds ratios for ESCC risk associated with oral hygiene (frequency, implement, oral charcoal use), DMFT score and level of dental staining with increasing levels of adjustment

	Controls N (col %)	Cases N (col %)	Model 1: all participants: 310 cases/313 controls OR_1 (95% CI)	Model 2: all participants: 310 cases/313 controls OR_2 (95% CI)	Model 2: never tobacco users: 94 cases/223 controls OR_{2a} (95% CI)
Daily tooth brusher	304 (97.1)	259 (83.6)	1	1	1
Less than daily brusher	9 (2.9)	51 (16.5)	4.79 (2.25, 10.22)	2.77 (1.2, 6.43)	4.45 (1.05, 18.85)
Brushing implement[a]					
Modern toothbrush	285 (91.4)	203 (66.1)	1	1	1
Chewed stick	25 (8.0)	100 (32.6)	4.68 (2.81, 7.78)	2.28 (1.27, 4.09)	2.77 (1, 7.65)
Other	2 (0.6)	4 (1.3)	—		
Use of charcoal to clean teeth					
Never	278 (88.8)	214 (69.0)	1	1	1
Ever user but not daily	27 (8.6)	77 (24.8)	3.63 (2.20, 6.00)	2.33 (1.33, 4.07)	2.16 (0.94, 4.93)
Daily	8 (2.6)	19 (6.1)	3.61 (1.48, 8.78)	2.11 (0.81, 5.5)	2.12 (0.51, 8.79)
Missing teeth					
0	137 (43.8)	90 (29.0)	1	1	1
1 or 2	77 (24.6)	77 (24.8)	1.48 (0.95, 2.31)	1.15 (0.69, 1.93)	1.38 (0.65, 2.95)
3 to 5	65 (20.8)	57 (18.4)	1.20 (0.73, 1.96)	1.07 (0.61, 1.88)	2.26 (1.04, 4.91)
6+	34 (10.9)	86 (27.7)	3.49 (2.06, 5.92)	2.58 (1.4, 4.75)	3.79 (1.53, 9.39)
Filled teeth					
None	303 (96.8)	305 (98.4)	1	1	1
1 or more	10 (3.2)	5 (1.6)	0.40 (0.12, 1.30)	0.35 (0.08, 1.45)	0.15 (0.01, 0.6)
Decayed teeth					
0	180 (57.5)	137 (44.3)	1	1	1
1 or 2	64 (20.5)	72 (23.3)	1.57 (1.02, 2.41)	1.29 (0.78, 2.14)	1.53 (0.74, 3.16)
3 to 4	32 (10.2)	38 (12.3)	1.41 (0.81, 2.45)	1.51 (0.77, 2.95)	1.71 (0.68, 4.29)
5+	37 (11.8)	62 (20.1)	2.87 (1.69, 4.86)	2.63 (1.43, 4.83)	2.9 (1.23, 6.86)
DMFT[b] index					
0	123 (39.3)	62 (20.1)	1	1	1
1 to 3	66 (21.1)	81 (26.2)	2.58 (1.60, 4.16)	1.7 (0.98, 2.95)	2.1 (0.95, 4.66)
4 to 9	80 (25.6)	73 (23.6)	1.63 (1.01, 2.65)	1.32 (0.75, 2.32)	2.28 (1.05, 4.98)
10+	44 (14.1)	93 (30.1)	4.26 (2.51, 7.24)	3.26 (1.77, 6.02)	3.88 (1.6, 9.39)
TFI fluorosis index assessed by nondental observer[c]					
0 (no fluorosis)	106 (33.9)	29 (9.5)	1	1	1
1	75 (24.0)	42 (13.8)	2.19 (1.19, 4.02)	2.38 (1.21, 4.68)	1.24 (0.51, 3.04)
2	47 (15.0)	42 (13.8)	3.60 (1.89, 6.88)	2.88 (1.4, 5.92)	1.66 (0.61, 4.51)
3	36 (11.5)	43 (14.1)	4.63 (2.34, 9.19)	2.65 (1.23, 5.72)	3.47 (1.16, 10.35)
4	37 (11.8)	70 (23)	8.30 (4.37, 15.79)	3.51 (1.72, 7.13)	4.15 (1.44, 11.94)
5+	12 (3.8)	78 (25.7)	27.1 (12.2, 60.3)	13.47 (5.7, 31.9)	13.9 (4.1 47.33)

[a]Other is combined with chewed stick for the odds ratios (1 missing value).
[b]DMFT = decayed + missing + filled tooth count.
[c]Thylstrup-Fejerskov index (TFI), which excludes six participants (all cases) as five were edentulous and one case not possible to evaluate; Model 1: adjusted for age and education (continuous) and indicators for sex, region/district and Chagga ethnicity; Model 2: adjusted for Model 1 factors, alcohol use (current, past, never) and tobacco use (never, smokeless only, smoking only, smoking and smokeless).

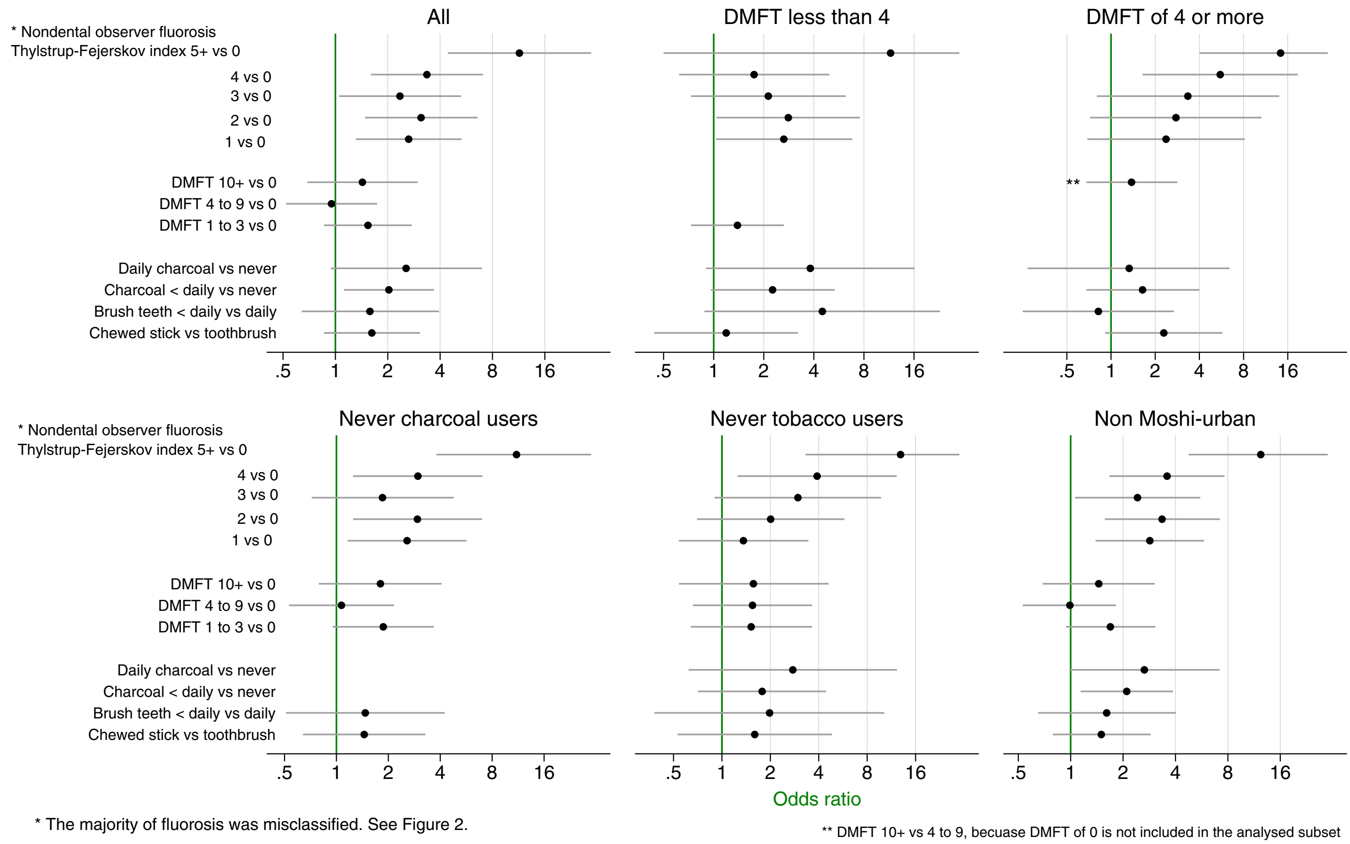

FIGURE 3 Odds ratios (ORs) for oral hygiene, DMFT and nondental observer-assessed fluorosis in relation to ESCC risk, overall in a risk-factor defined subsets (values are provided in Supplementary Table 1). ORs are mutually adjusted for age, sex, region of residence, Chagga ethnicity, education, alcohol, tobacco and for all the oral health indicators included in the figure

number of missing and decayed teeth were low (median of 2 or less) and filled teeth were rare; therefore, DMFT scores were low in controls (mean 4.6 [95% CI: 4.4, 4.9]). Median nondental observer-assessed TFI was also low (median score of 1, mean 1.6 [1.4, 1.8]). Other than daily tooth brushing and filled teeth, there was sufficient heterogeneity to examine correlates of oral health/hygiene features (Table 2). Oral charcoal use was more common in women, in the less educated and in drinkers/tobacco users. Not using a modern toothbrush was also more common in drinkers/tobacco users and in rural residents (ie, non-Moshi-urban district). These oral hygiene habits were not associated with age, contrasting to the increased number/level of missing/decayed teeth, DMFT index and nondental observer-assessed TFI in older controls. Nondental observer-assessed TFI was also associated with lower education, lack of toothbrush use and strongly associated with tobacco use. Chagga people had lower DMFT scores than other ethnic groups.

3.4 | Oral hygiene and DMFT in relation to ESCC risk

Odds ratios for ESCC associated with oral hygiene and health status are provided in Table 3 (Models 1 and 2). Lack of daily tooth brushing, brushing with a chewed stick toothbrush and ever use of oral charcoal were associated with OR_2 of 2 to 3 (ie, adjusted for design factors, alcohol and tobacco). These associations held overall and in never tobacco users (OR_{2a}). The effects for chewed stick toothbrush use and nondaily brushing attenuated to an OR_3 of 1.5 to 1.6 (nonsignificant) upon adjustment for DMFT score and nondental TFI score. In contrast, OR_3 for oral charcoal use remained at 2.0 (1.1-3.7), but there was no suggestion of a dose-response relationship with frequency of oral charcoal use, albeit with few daily oral charcoal users.

Having six or more missing teeth compared to no missing teeth was associated with increased ESCC risk (OR_2 2.6 [95% CI: 1.4, 4.8]). An association of similar magnitude was seen for at least five decayed teeth (OR_2 2.6 [1.4, 4.8]). Thus, for the composite DMFT index, a score of 10 or greater was associated with an OR of 3.3 (1.8-6.0). Having filled teeth was associated with reduced ESCC risk, but fillings were rare in the current study (<3%). The effects of missing, decayed or DMFT with ESCC risk were marginally stronger in never tobacco users (OR_{2a}); however, they were strongly attenuated after adjusting for nondental observer assessed TFI to an OR_3 of 1.4 (0.7, 3.0) for DMFT of 10+ compared to people with a DMFT of 0.

Concerning the nondental observer-assessed TFI, albeit keeping in mind that only a small proportion is actually fluorosis (Figure 1), associations are summarized first for the findings in the range of TFI 0 to 4 and then separately for TFI 5+ compared to 0. For TFI 1 to 4 compared to no fluorosis (0), stepwise increases in ESCC risk were present (OR_1) in crude analyses, which halved in magnitude upon adjustment for tobacco and alcohol use to an OR_2 of 3.5 (1.7-7.1) for TFI 4 vs 0. This effect was present in never-tobacco users (OR_{2a}) and persisted upon adjustment for DMFT score and oral hygiene (OR_3 in Figure 3). However, as shown in Figure 3 (Supplementary Table 1), when restricted to non-Moshi residents, never oral charcoal users or DMFT<4, ESCC risks differed between those with TFI index 1 compared to 0 ($OR_{3b/d/e}$ of 2.6-2.9) and therafter plateaued for TFI 1 to 4. Nondental observer-assessed TFI of 5+ was present in 78 cases (25%) compared to 12 controls (4%) (Table 3). The resulting crude OR_1 was 27 for TFI 5+ vs 0, which was strongly attenuated upon controlling for tobacco use (OR_2 = 13.5). Nevertheless, the association was also present in never tobacco users (OR_{2a} 13.9) and was only slightly attenuated upon adjustment for oral hygiene and DMFT score (OR_3 12.9). The association also held in the further subsets examined (Figure 3, Supplementary Table 1) including for DMFT<4, in never oral charcoal users and after excluding participants from Moshi urban.

4 | DISCUSSION

4.1 | Principal findings

As part of etiological research on esophageal squamous cell carcinoma (ESCC) in the high-ESCC incidence region of East Africa, in 2019 Menya et al reported on a strong association of ESCC risk in western Kenya with poor oral hygiene, high DMFT scores and increased dental fluorosis grade.[18] In the present study, from the same ESCCAPE case-control studies and following the same protocol, we examined these associations in the neighboring country of Tanzania, in the Kilimanjaro region's first ESCC case-control study. Similar to the Kenyan findings, we found increased ESCC risks associated with higher DMFT scores and with the use of a chewed stick toothbrush and charcoal (*mkaa*) for cleaning teeth. With respect to dental fluorosis, a dentist's independent evaluation of dentition photographs revealed concerns regarding the fluorosis assessment by nondental observers. Explicitly the dentist considered that the majority of "fluorosis" was in fact extrinsic staining not of a fluorosis origin. We therefore need to interpret higher levels of the nondental-observer TFI index with caution, as the exposure assessed appears to have been a mix of real fluorosis, extrinsic staining present for a long duration or extrinsic staining recently acquired (in cases) due to changes in oral hygiene. Nevertheless, this nondental-observed "TFI" was very strongly associated with ESCC risk, like in Kenya, and, as will be expanded upon later, possible explanations for these associations must be viewed in light of these concerns of misclassification of fluorosis and the case-control design.

4.2 | Oral hygiene, decayed and missing teeth

Similar to the present findings from Tanzania, ESCC has been linked to poor oral hygiene and tooth decay/missing teeth in Kenya, Iran, China and Kashmir[10-12,18] and to edentulous EC patients in South Africa.[29] Although the present results revealed similar risk gradients to those previously observed, like in Kenya,[18] the population-level distributions of DMFT counts were much better (lower) in this setting than in the other high-risk populations.[10] These lower counts are possibly due to improved oral hygiene and lower sugar intake in East Africa. Alternatively, our assessment of the number of decayed teeth could have been underestimated since they were conducted by nondentists. The magnitude of DMFT-ESCC associations was of a smaller magnitude to those in Kenya,[18] but still strong (up to an OR of 4).

Poor oral hygiene has not been evaluated by the IARC monographs as to its carcinogenicity in humans but has recently been recommended among the priorities for future evaluation.[30] In the present study, data on three integral setting-relevant features were collected. These were frequency of tooth cleaning, cleaning implement (discussed separately below due to its different hypothesized biological mechanisms) and use of charcoal when cleaning teeth. Almost all participants practiced daily oral hygiene and thus there was no possibility to examine the impact of brushing frequency on ESCC risk. Concerning brushing implement, prevalence of chewed stick toothbrush use among Tanzanian controls was consistent with population surveys[31] but was lower than that in Kenya. Nevertheless, the chewed stick toothbrush-ESCC findings mirrored those from the ESCCAPE Kenyan study.[18] In the present study, it is noteworthy that chewed stick toothbrush users had raised ESCC risks in crude analyses due to their higher prevalence of the established ESCC risk factors of alcohol, tobacco use and lower socioeconomic position. However, the attenuated chewed stick toothbrush-ESCC associations remained significant having controlled for these positive confounders and in subgroup analyses among never tobacco users. Finally, the near-full attenuation of this association upon further adjustment for DMFT is likely to point to a common mediating pathway. Multiple mechanistic pathways linking oral health to ESCC are being investigated. They may involve alteration of the oral microbiome to a milieu with procarcinogenic properties or carcinogenic by-products. This could possibly be through production of acetaldehyde, reduction of nitrates to nitrites and their conversion to nitrosamines or increased bacterial species to produce reactive oxygen species among which are esophageal carcinogens.[32] Alternative pathways may include reduced mastication leading to physical damage to the esophagus or a role of chronic inflammation not only for ESCC but also for other upper GI cancers and liver cancer.[11]

Activated charcoal is claimed to be a detoxifying and cleansing agent for the skin and for tooth whitening due to its adsorption properties, akin to its use in air and water filters. The use of heated crushed charcoal for tooth whitening is common practice in rural Tanzania. Previous surveys in the neighboring region to Kilimanjaro, Tanga, found 11% prevalence of charcoal use orally, which is consistent with the present study's estimate in controls.[31] Although a positive association of charcoal with ESCC risk was found in the present study, a dose-response relationship was not observed but exposure assessment was extremely crude. Oral charcoal use has the potential for exposure to ingested polycyclic aromatic hydrocarbons (PAHs), chemicals whose role in ESCC has already been well established in a unique esophageal tissue-based case-control study in Iran.[33] With considerable oral charcoal use especially in women (20% vs 8% in male controls), further research is needed to better characterize this habit in terms of frequency, ingested dose, its association with ESCC and possibly oral cancers.

4.3 | Dental fluorosis and false-positive fluorosis

Although the dental photographs taken were unfortunately too low in quality to enable an independent assessment of the full TFI index, the professional dentist considered that majority of nondental observer assessed "fluorosis" was extrinsic staining and did not have a dental fluorosis origin. This critical observation led us to interpret the measured trait as dentition staining of unspecified origin for the purpose of this discussion. Extrinsic dental staining in the set of photographs consisted of a combination of problems. They included crown dental caries, calculus and root decay. In agreement with the presence of considerable fluorosis misclassification, and this interpretation as extrinsic staining, in controls the assessed trait was strongly associated with older age, tobacco use and use of a chewed stick for oral hygiene. Dental staining of nonfluorosis origin is expected in this study owing to the older age of participants who have accumulated a lifetime of exposures in a population where dentists are few. Nevertheless, assuming no underreporting of tobacco use, tobacco stains would not fully account for the association with dental staining, because the latter's association with ESCC held among never tobacco users. Other factors compromising dentition development in the Tanzania setting are malnutrition and serious illnesses during childhood. The resulting dentition developmental disturbances could also be mistaken for fluorosis by nonexperts. In future studies, professional assessment of fluorosis, with physical examination and cleaning, will be necessary on all participants. Our study would also have benefitted from asking the participant if they had stained teeth when they were younger, say at age 20. Without a professional dentists assessment, as can be seen in Supplementary Figure 2, the untrained eye focuses on stains rather than pitting, leading to misclassification. There also remains the strong likelihood that extrinsic staining develops or intensifies in the few months prior to diagnosis among cases who are symptomatic and experiencing dysphagia and xerostomia (dry mouth), which is typical of this setting. In the present study, the median (IQR) time with dysphagia prior to diagnosis was 2 months (2-3). If normal oral hygiene practices are interrupted during this period, plaque will form rapidly. Plaque contains a bacterial community including chromogenic bacteria, which cause extrinsic stains. Extrinsic black plaque has been found to be associated with poor oral hygiene, snacking between meals, iron supplements and drinking water with high iron content and pH levels.[34]

In light of the above discussion, while the dental staining-ESCC association could partially reflect true increased ESCC risks via a similar mechanism as tooth decay and periodontal disease, the very large odds ratio at the highest level of staining may also be partly due to reverse causality. In the absence of the ability to perform a physical examination to separate fluorosis from extrinsic staining and the absence of a history of extrinsic staining, the present study design cannot possibly disentangle the extents of these possible exposure origins and biases. Finally, the current results have implications for the interpretation of our previously reported strong association of ESCC with dental fluorosis in Kenya[18] for which a similar effect of misclassification cannot be ruled out, because diagnosis is similarly late and good oral hygiene practices may have ceased. Indeed, in that study, the restriction of the "fluorosis"-ESCC association to participants having higher DMFT counts would be consistent with this same misclassification mechanism.

4.4 | Strengths and limitations

Our current Tanzanian case-control study of ESCC has several general commendable features. It is the first such study on ESCC in this high-risk region of the country. The case-control study design included histological confirmation of cases for the majority who attended KCMC and a high participation percentage. The challenge of recruiting an appropriate control group was addressed through inclusion of two control types—hospital patients and hospital visitors—and the challenge of more controls than cases residing close the central recruitment center was addressed in an analysis excluding all residents of the local district. Although not all cases were histologically confirmed and were instead included on the basis of symptoms, inclusion of these cases is standard in ESCC studies in Africa. Their inclusion is unlikely to have led to major outcome misclassification due to the specificity of symptoms in this setting[25] and the predominance of ESCC in the EC burden.[26] Concerning the specific oral health assessment, the study was strengthened by a photographic validation on a subset, which provided a crude assessment of the nondental observer's TFI. However, in addition to the low quality of photographs, they included fewer controls than cases. Nevertheless, the overall impression that a majority of the staining being evaluated was extrinsic and not of a fluorosis origin is a critical observation and led to an important interpretation of exposure assessment. For the DMFT count, we should have had a separate count of missing teeth due to accidents, rites of passage or other cultural practices than from health problems. Furthermore, a reported history of oral hygiene does not always correlate with actual habits and we lacked the inability to examine temporality of the exposure-outcome relationship.

4.5 | Public health and research implications

The findings point to the potential toward primary prevention of ESCC in Tanzania through an incremental contribution of improved oral health and oral hygiene. Further research is first needed to evaluate more definitively the causal effects on ESCC of chewed stick toothbrush use and charcoal to clean teeth. This will need epidemiological, exposure and mechanistic studies. Concerning links of ESCC to oral hygiene habits, higher DMFT and extrinsic dental staining, detailed oral health exposure measurement studies including physical examinations by dentists, with a broader assessment of features of oral health (eg, of calculus, plaque, periodontal disease, oral hygiene index) are warranted. Such an exposure assessment implemented in a case-control design will not overcome the problem of temporality, thus in the absence of suitable cohort studies in this setting, cross-sectional studies—albeit imperfect—may offer the best possible timely design. Such studies have been conducted by Mwachiro et al in Tenwek, Kenya.[35] In that study detailed exposures were correlated with prevalent chromoendoscopy-assessed dysplasia, which is a precursor to ESCC. Cross-sectional studies in higher-risk populations or analytical exposure-stratified cross-sectional studies, which include a detailed oral health assessment, may have a role in investigating the distinct effect of oral health status and oral hygiene on these esophageal precursors. For the same endpoint, another attractive appropriate health technology being investigated for its potential use in East Africa is the Cytosponge device[36] developed by the Fitzgerald Lab at the Cambridge MRC Cancer Unit. This sponge encapsulated in a pill-on-a-string collects esophageal epithelial cells less invasively than through endoscopy, thus may have an important role to play in ESCC research and in early detection in low resource settings. Notably, in a cross-sectional study of esophageal dysplasia in relation to oral health, there would be fewer concerns of reverse causality in relation to dental staining. Furthermore, and notwithstanding the abovementioned concerns on etiological pathways, the possibility that dental staining might be useful in the identification of high-risk individuals warrants investigation. Notably the strong OR values of 8 and 27 (Model 1) were accompanied by substantial case prevalence of 23% (staining level 4) and 26% (staining level 5), respectively.

Eastern Africa's current esophageal cancer burden of 19 000 new cases in 2020 will increase to 28 000 new cases by 2030, with almost as many deaths as new cases annually (1). For prevention of this burden, improvements in oral hygiene and oral health may have a role to play among the multifactorial risk factors for this disease.

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CONFLICT OF INTEREST

The authors declare no completing interests. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

DATA AVAILABILITY STATEMENT

Data can be accessed via collaboration with IARC (https://esccape.iarc.fr/en/Contact).

ETHICS STATEMENT

The ESCCAPE Tanzania case-control study is a Kilimanjaro Clinical Research Institute and International Agency for Research on Cancer (IARC) collaboration. It was approved by the following ethics institutions: National Institute for Medical Research Tanzania (NIMR/HQ/R.8a/Vol.IX/1994) and the IARC Ethics Committee (IEC 14/15) and Tumaini University Kilimanjaro Christian Medical University College (830). All participants provided written informed consent for study participation in the local language, Kiswahili, after the study was explained to them and information sheets provided.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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