original reports abstract

Risk Factors Associated With Early-Onset Esophageal Cancer in Tanzania

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PURPOSE Eastern Africa is one of several regions affected by high incidence rates of esophageal squamous cell carcinoma (ESCC). A unique epidemiologic feature of ESCC in Eastern Africa is the high incidence in young people, with one-third of cases diagnosed at age < 45 years. This study aimed to investigate risk factors for early-onset ESCC in Tanzania through a secondary analysis of a matched case-control study.

MATERIALS AND METHODS From 2013 to 2015, ESCC cases were recruited at Muhimbili National Hospital and Ocean Road Cancer Institute in Dar es Salaam, Tanzania. Hospital controls were identified from patients with nonmalignant conditions and matched 1:1 for sex and age (± 10 years). Questionnaires were used to assess sociodemographic characteristics and environmental, dietary, and lifestyle risk exposures. Multivariate logistic regression models were used to estimate age-specific odds ratios of ESCC for exposures among participants age 30-44 and ≥ 45 years.

RESULTS A total of 471 cases and 471 controls were enrolled. Among cases, 100 (21%) were < 45 years. Multiple exposures were identified as risk factors for early-onset ESCC, several of which were unique to this age group, including infrequent teeth cleaning, secondhand tobacco smoke exposure, and pest infestation of grain and/or nuts. Lower socioeconomic status, family history of ESCC, tobacco smoking, home-brewed alcohol consumption, home storage of grain and/or nuts, and use of firewood for cooking were associated in the older but not the younger age group. Hot beverage intake was associated with increased ESCC risk in both age groups.

CONCLUSION Our results suggest that ESCC risk factors in Tanzania vary between age groups. With the data currently available, environmental and behavioral risk factors appear to play an important role in the high incidence of ESCC among young people.

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INTRODUCTION

Esophageal cancer (EC) is a leading cause of cancer mortality globally.[1] EC is notable for distinct geographic variations in incidence rates and histologic subtypes. Esophageal squamous cell carcinoma (ESCC) accounts for the majority of EC cases in low- and middle-income countries, whereas esophageal adenocarcinoma is the most common histology in high-income countries.[2] High-incidence clusters of ESCC have been identified in north-central China, northeastern Iran, southern South America, Central Asia, and Eastern Africa.[3,4]

Research from Asia and South America has established a number of risk factors for ESCC in these settings, including tobacco and alcohol use, low socioeconomic status, pickled vegetables, and hot foods.[5] Etiologic factors underlying the high incidence in Eastern Africa, however, remain poorly understood.

A unique feature of ESCC in Eastern Africa is the high proportion of patients diagnosed at young ages.[3] In the United States, 2% of cases are < 45 years.[6] Similar proportions have been reported in high-incidence regions.[7,8] By contrast, studies from Eastern Africa have reported that up to one-third of all incident cases are < 45 years at diagnosis.[3,9-16]

In effort to evaluate this disproportionate burden of early-onset ESCC in Eastern Africa, we aimed to investigate possible associations of sociodemographic characteristics and environmental, dietary, and lifestyle risk factors. To our knowledge, this is the first epidemiologic analysis of age-specific risk factors for ESCC in Eastern Africa.

MATERIALS AND METHODS

Study Design

This is a secondary analysis of a matched case-control study designed to evaluate potential risk factors for ESCC in Tanzania. The study design and methods of the original study including case definitions and recruitment procedures were previously published.[17]

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What sociodemographic characteristics and environmental, dietary, and lifestyle risk factors are associated with early-onset (age 30-44 years) versus later-onset (age ≥ 45 years) esophageal squamous cell carcinoma (ESCC) in Tanzania?

Knowledge Generated

Our findings suggest risk factors for ESCC in Tanzania may differ across age groups. Possible risk factors for early-onset ESCC (age 30-44 years) include poor oral hygiene, prior pest infection of stored grain and/or nuts, hot beverage intake, second tobacco smoke exposure, and permanent residence in the Northern Lake Zone of Tanzania. Low socioeconomic status, family history of ESCC, tobacco smoking, home-brewed alcohol consumption, home storage of grain and/or nuts, and use of firewood for cooking were found to be risk factors unique to the older age group (≥ 45 years).

Relevance

Key differences in risk factors for ESCC across the lifespan could have important implications for future etiologic studies and primary prevention efforts.

The objective of this secondary analysis was to investigate potential etiologic factors associated with early-onset ESCC in Tanzania.

Study Setting and Population

The case-control study was conducted at Muhimbili National Hospital (MNH) and Ocean Road Cancer Institute (ORCI) in Dar es Salaam, Tanzania. Eligible cases were patients with newly diagnosed ESCC from 2013 to 2015 who were age ≥ 30 years. Diagnostic criteria included patients with histologically confirmed ESCC and patients diagnosed clinically based on computed tomography scan, barium swallow, or endoscopy. We used expanded diagnostic criteria allowing for nonpathologically confirmed cases given the prohibitive costs of pathology. Previous data indicate that a clinical diagnosis of EC corresponds to ESCC with > 90% pretest probability in this setting.[10]

Eligible controls were identified from patients admitted to the MNH medical, surgical, trauma, and gynecology wards for a nonmalignant condition and were matched 1:1 with cases for sex and age (± 10 years). Nonpermanent residents of Tanzania were excluded from both groups.

Data Collection

Exposure data were collected through structured interviews, using questionnaires that captured established ESCC risk factors, and setting-specific putative risk factors. Full details on the standardized questionnaires were previously described.[17] Exposure variables included sociodemographic factors, residential history, occupational history and related exposures, medical history, family medical history, household exposures, dietary factors, and lifestyle risk behaviors. Interviews were conducted in Swahili by trained research assistants.

Ethics Statement

This study was approved by institutional review boards at Muhimbili University of Health and Allied Sciences (Dar es Salaam, Tanzania), the University of California, San Francisco (UCSF, San Francisco, CA), and the National Institute for Medical Research (NIMR) of Tanzania. Written informed consent was obtained from all participants before enrollment in Swahili, the national language of Tanzania.

Statistical Analysis

Study participants were categorized into two age groups: 30-44 years and ≥ 45 years. Descriptive statistics were used to summarize sociodemographic factors and exposure variables for cases and controls by age group. Within each age group, univariate logistic regression models were used to test for associations between each exposure and ESCC risk. The age-specific odds ratio (OR) of ESCC and the 95% Wald CI were calculated for each exposure.

Multivariate logistic regression modeling was then used to assess the independent effect of the exposures within each age group. A multivariate model was fit with inclusion of design factors (age, sex), sociodemographic characteristics (geographic zone and a composite measure of socioeconomic status calculated using the International Wealth Index [IWI][18]), retention of established ESCC risk factors,[5] and exposures that were significantly associated with ESCC in the age-stratified univariate analyses. Established risk factors included in the model were tobacco use (current or former use *v* never), alcohol use (current or former use *v* never), home-brewed alcohol consumption (current or former use *v* never), and daily hot beverage consumption (as a continuous variable). The same model was fit to the younger age group (30-44 years) and the older age group (≥ 45 years) to examine differences in risk factors and magnitudes of associations between the two age groups. Finally, the likelihood-ratio test (LRT) was used to assess if the effect of the risk factor differs between age groups. In this analysis, the LRT was used to compare nested models of the age-adjusted main-effect exposure data with a model that included an interaction term of the main-effect exposure on age group.

Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC). Statistical significance was declared based on a two-sided *P*-value $< .05$. No multiple testing adjustment was conducted across the exposures.

RESULTS

A total of 471 ESCC cases and 471 matched controls were included in the analysis.[17] Among cases, 21% were age 30-44 years, and 79% were age ≥ 45 years. Table 1 summarizes the sociodemographic characteristics of cases and controls by age group. Results of multivariate logistic regression analyses among the younger age group (30-44 years) and the older age group (≥ 45 years) are presented in Table 2. The univariate analyses of age-specific associations of ESCC and sociodemographic factors, behavioral risk factors, and household exposures that were used to inform variable selection in multivariate modeling are presented in Appendix Tables A1-A4.

Sociodemographic Factors

Zone of permanent residence emerged as a risk factor in multivariate models in younger and older groups. Among the younger group, residence in the Northern Lake Zone was associated with increased risk of ESCC (adjusted OR [aOR] 12.06; 95% CI, 3.18 to 45.71). Among the older age group, residence in the Northern Lake Zone (aOR 1.57; 95% CI, 1.02 to 2.41) and the Southern Highlands-Central zone (aOR 3.24; 95% CI, 1.94 to 5.41) were each associated with increased risk. The effect of zone differed significantly between age groups (LRT *P*-value = .01).

Among the older age group, an IWI score in the middle or lowest tertile was associated with increased ESCC risk (low IWI: aOR 1.89; 95% CI, 1.19 to 3.01; middle IWI: aOR 1.75; 95% CI, 1.11 to 2.76). There was a similar trend among the younger age group; however, this was not statistically significant after controlling for other exposures. Family history of EC was associated with an increased risk in the older (aOR 4.03; 95% CI, 1.36 to 11.98) but not the younger age group, with a significant difference in effect between age groups (LRT *P*-value = .02).

Behavioral Risk Factors

None of the lifestyle risk behaviors investigated, including consumption of alcohol, home brew, or tobacco smoking, were associated with increased ESCC risk in the younger age group. Among the older age group, smoking tobacco was associated with increased ESCC risk (aOR 2.04; 95% CI, 1.33 to 3.12). In evaluating alcohol consumption among the older group, paradoxically, current or former use of any type of alcohol appeared to have a protective effect (aOR 0.39; 95% CI, 0.23 to 0.65). Consumption of home-brewed alcohol in particular (current or former use of any type), by contrast, was associated with increased risk (OR 2.08; 95% CI, 1.26 to 3.41).

Less than daily teeth cleaning was associated with increased ESCC risk in the younger group (aOR 9.79; 95% CI, 1.90 to 50.54), but not the older age group. Intake of an increasing number of hot beverages daily was associated with increasing ESCC risk in a dose-response relationship among both age groups (younger: aOR 1.99; 95% CI, 1.13 to 3.50; older: aOR 1.60; 95% CI, 1.13 to 2.27). Daily consumption of raw greens was found to be protective in both age groups (younger: aOR 0.20; 95% CI, 0.05 to 0.88; older aOR 0.44; 95% CI, 0.23 to 0.85).

Household Exposures

Secondhand tobacco smoke in the home was associated with an increased risk of ESCC among the younger (aOR 2.58; 95% CI, 1.00 to 6.67) but not the older group. Firewood cooking was associated with increased ESCC risk among the older group (aOR 1.54; 95% CI, 1.00 to 2.37), but not the younger group. In-home storage of grain and/or nuts was associated with increased risk among the older group (aOR 1.68; 95% CI, 1.05 to 2.70), but not the younger group. Previous pest infection of grain and/or nuts was associated with increased risk of ESCC among the younger group (aOR 4.00; 95% CI, 1.38 to 11.59), but not the older group.

DISCUSSION

In this analysis, multiple exposures were identified as potential risk factors for early-onset ESCC, including poor oral hygiene, pest infection of grain and/or nuts, hot beverage intake, secondhand tobacco smoke exposure, and permanent residence in the Northern Lake Zone of Tanzania. Overall, we found that risk factors varied in their effect among different age groups. These findings suggest that the relative importance of certain risk factors for ESCC in Eastern Africa may vary across the lifespan, likely because of differences in exposure patterns by age and/or latency of effect.

To our knowledge, this is the first analytic epidemiologic study of risk factors for early-onset ESCC in Eastern Africa. Findings from this study build on earlier work from Western Kenya, which first looked into unique epidemiologic patterns that may explain the high incidence of ESCC among young people in this region.[16,19] One case series included a comparative analysis of sociodemographic characteristics of patients age ≤ 30 and > 30 years. In this study, Kalenjin ethnicity appeared to confer increased ESCC risk at early ages, whereas geographic region and sex both had null effect.[16] A subsequent case series from the same institution assessed alcohol and tobacco use and family history of EC in 60 cases age ≤ 30 years.[19] Nearly half of cases had a family history of EC. Neither tobacco use nor alcohol use was common among cases.

Prior findings from Kenya of increased risk of ESCC with a specific ethnicity and with a family history of EC suggest the possibility of underlying genetic susceptibility and/or shared environmental exposures. In our analysis, family history emerged as a risk factor, but only among the older group. Although comparisons are limited by age differences

TABLE 1. Sociodemographic Factors by Age Group

Sociodemographic Factor	Younger Group (age 30-44 years)			Older Group (age ≥ 45 years)		
	Cases (n = 100), No. (%)	Controls (n = 108), No. (%)	*P*	Cases (n = 371), No. (%)	Controls (n = 363), No. (%)	*P*
Sex			.674			.848
Male	62 (62)	70 (65)		262 (71)	254 (70)	
Female	38 (38)	38 (35)		109 (29)	109 (30)	
Ethnicity			.999			.135
Arab	0	0		0	2 (< 1)	
White	0	0		2 (< 1)	0	
African	100 (100)	108 (100)		369 (99)	361 (99)	
Zone			**< .001**			**< .001**
Coastal-Zanzibar	58 (58)	95 (88)		167 (45)	248 (69)	
Central	7 (7)	4 (4)		53 (14)	17 (5)	
Lake	3 (3)	3 (3)		19 (5)	31 (9)	
Northern	24 (24)	2 (2)		84 (23)	40 (11)	
Southern Highlands	8 (8)	4 (4)		45 (12)	21 (6)	
Unknown				3	6	
Education			**.003**			**< .001**
None	8 (8)	3 (3)		84 (23)	45 (12)	
Any primary level	75 (75)	63 (58)		242 (66)	209 (58)	
Any secondary	10 (10)	28 (26)		29 (8)	71 (20)	
Postsecondary or above	7 (7)	14 (13)		14 (4)	38 (10)	
Unknown				2		
Occupation			**.002**			**< .001**
Agriculture	40 (40)	21 (19)		210 (57)	121 (33)	
Business	19 (19)	30 (28)		26 (7)	54 (15)	
Office work	3 (3)	13 (12)		29 (8)	48 (13)	
Other	38 (38)	44 (41)		106 (29)	139 (38)	
Unknown					1	
Household income, TSH			**.048**			**< .001**
< 150,000	8 (11)	1 (< 1)		17 (6)	14 (5)	
150,001-500,000	7 (9)	8 (10)		48 (17)	27 (9)	
500,001-900,000	16 (21)	15 (19)		69 (25)	48 (17)	
900,001-1,200,000	17 (23)	13 (16)		62 (22)	45 (16)	
> 1,200,000	27 (36)	43 (54)		80 (29)	153 (53)	
Unknown	25	28		95	76	
IWI[a]			**.005**			**< .001**
High (67-100)	24 (25)	48 (45)		71 (20)	164 (46)	
Medium (33 ≤ 67)	42 (43)	40 (37)		126 (35)	95 (27)	
Low (0 ≤ 33)	31 (32)	19 (18)		165 (46)	95 (27)	
Unknown	3	1		9	9	
Family history of EC			.241			**< .001**
No	97 (97)	101 (94)		338 (93)	351 (99)	
Yes	3 (3)	7 (6)		24 (7)	5 (1)	
Unknown				9	7	

NOTE. Statistically significant findings are highlighted as bold text.

Abbreviations: EC, esophageal cancer; IWI, International Wealth Index; TSH, Tanzanian Shillings.

[a]IWI[18] scores range from 0 to 100 (low to high) and are calculated based on nine consumer durables or housing characteristics, including television, refrigerator, telephone, radio, washing machine, toilet, floor material, electricity, and drinking water source.

TABLE 2. aORs and 95% CIs of Independent Risk Factors for ESCC on the Basis of Multivariate Logistic Regression Within Each Age Group

	Younger Group (age 30-44 years)	Older Group (age ≥ 45 years)	
Risk Factor	**aOR (95% CI)**	**aOR (95% CI)**	***P*[a]**
Sex			.198
Male	1	1	
Female	1.58 (0.65 to 3.83)	1.23 (0.80 to 1.88)	
Age at diagnosis (+1 year)	1.05 (0.95 to 1.15)	1.01 (0.99 to 1.02)	
Zone			**.011**
Coastal-Zanzibar	1	1	
Northern Lake Zone	**12.06 (3.18 to 45.71)**	**1.57 (1.02 to 2.41)**	
Southern Highlands-Central	1.96 (0.62 to 6.26)	**3.24 (1.94 to 5.41)**	
IWI[b]			.921
High (67-100)	1	1	
Medium (33 ≤ 67)	1.41 (0.58 to 3.44)	**1.75 (1.11 to 2.76)**	
Low (0 ≤ 33)	2.78 (0.90 to 8.53)	**1.89 (1.19 to 3.01)**	
Family history of EC			**.022**
No	1	1	
Yes	0.49 (0.05 to 4.50)	**4.03 (1.36 to 11.98)**	
Smoking tobacco (current or former use)			.123
No	1	1	
Yes	0.79 (0.29 to 2.11)	**2.04 (1.33 to 3.12)**	
Alcohol (any type; current or former use)			.958
No	1	1	
Yes	0.52 (0.22 to 1.26)	**0.39 (0.23 to 0.65)**	
Home-brewed alcohol (any type; current or former use)			.375
No	1	1	
Yes	1.64 (0.57 to 4.72)	**2.08 (1.26 to 3.41)**	
Secondhand tobacco smoke in the house			.201
No	1	1	
Yes	**2.58 (1.00 to 6.67)**	1.35 (0.87 to 2.09)	
Firewood cooking in home			.721
No	1	1	
Yes	1.21 (0.51 to 2.88)	**1.54 (1.00 to 2.37)**	
How often teeth cleaned			.157
Daily	1	1	
Less than daily	**9.79 (1.90 to 50.54)**	1.55 (0.99 to 2.41)	
Grain and/or nuts preserved			.727
No	1	1	
Yes	1.05 (0.42 to 2.65)	**1.68 (1.05 to 2.70)**	

(Continued on following page)

between study populations given our exclusion of cases age < 30 years, our findings argue against genetic factors contributing to the high burden of early-onset disease; however, this warrants further exploration and will be addressed by the multisite genome wide association study currently underway.

In our study, we detected an increased risk of ESCC with a dose-response to frequency of hot beverage intake in both age groups. Other metrics investigating hot beverage exposure (preferred beverage temperature, number of times burnt tongue or mouth) showed no age-specific effects. The results differ slightly from previous case-control studies in Kenya, although comparisons are limited by the lack of harmonized exposure metrics.[20,21] In one study, a preference for hot beverages was associated with ESCC.[21] In another study, self-reported consumption of very hot beverages was associated with increased ESCC risk; however, other metrics of exposure, including daily number of hot beverages, had no significant effects.[20] While findings across studies have been inconsistent thus far, our analysis suggests that frequent hot beverage consumption may increase risk of early-onset disease.

The potential role of poor oral health as a risk factor for ESCC in Eastern Africa has recently gained attention.[21-23] Contemporaneous case-control studies in Kenya and Northern Tanzania found that infrequent teeth cleaning and the presence of missing and decayed teeth were associated with increased ESCC risk.[22,23] Comparable findings have been reported in China and Iran.[24-29] Possible mechanisms of carcinogenesis include chronic inflammation in the setting of periodontal disease and/or changes in the oral microbiome leading to carcinogenic metabolite byproducts.[30] Our analysis is the first to evaluate age-specific effects of oral health on ESCC risk. We found that infrequent tooth brushing was associated with an increased risk of early-onset ESCC, whereas tooth loss had null effect. Among the older group, infrequent tooth brushing and tooth loss were associated with ESCC risk in the univariate but not the multivariate analyses. It is unclear why the effects of both exposures attenuated in the multivariate model; however, one possible explanation is that the protective effects of oral hygiene may diminish with older age as oral health conditions become more prevalent (ie, caries, gingivitis, periodontal disease, etc). These dimensions of oral health were beyond the scope of the current study. Additional research is needed to further investigate the relationship between oral health and ESCC risk in Eastern Africa.

Several dietary factors appeared to influence the risk of early-onset ESCC in our analysis, including the protective effects of raw green intake and prior pest infection of stored grain and/or nuts. Raw green consumption was similarly protective in the oldest group, whereas practices of

TABLE 2. aORs and 95% CIs of Independent Risk Factors for ESCC on the Basis of Multivariate Logistic Regression Within Each Age Group (Continued)

	Younger Group (age 30-44 years)	Older Group (age ≥ 45 years)	
Risk Factor	**aOR (95% CI)**	**aOR (95% CI)**	***P*[a]**
Grain and/or nuts has been infected by pests			.171
No	1	1	
Yes	**4.00 (1.38 to 11.59)**	1.03 (0.66 to 1.60)	
How many hot beverages daily			.538
+1 hot drink daily	**1.99 (1.13 to 3.50)**	**1.60 (1.13 to 2.27)**	
Consumption of raw greens			.659
Less than daily	1	1	
Daily	**0.20 (0.05 to 0.88)**	**0.44 (0.23 to 0.85)**	

NOTE. Statistically significant findings are highlighted as bold text.

Abbreviations: aOR, adjusted odds ratio; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; IWI, International Wealth Index; LRT, likelihood-ratio test.

[a]LRT to assess if the effect of the risk factor is different between age groups.

[b]IWI[18] scores range from 0 to 100 (low to high) and are calculated based on nine consumer durables or housing characteristics, including television, refrigerator, telephone, radio, washing machine, toilet, floor material, electricity, and drinking water source.

preserving grain and/or nuts were associated with increased ESCC risk in this group. Many studies have explored the relationship between dietary factors and ESCC, and raw fruit and vegetable intake has consistently been shown to have protective effects.[5,31] Our findings related to household storage practices of grain and/or nuts raise the question of whether undetected contaminants or infestations may play a causative role. Further research into this exposure will likely require field study.

The geographic variability of ESCC incidence rates, globally and regionally, has been the focus of a large body of research investigating ESCC risk factors. In our study, permanent residence in the Central, Northern Lake Zone, or Southern Highlands geographic areas was found to be associated with an increased ESCC risk in non–age-stratified analyses.[17] The Northern Lake Zone area emerged as the only area associated with increased risk among the youngest age group, with a strong magnitude of association, albeit with a wide CI due to small sample size. With MNH and ORCI both located in the Coastal zone, some of the elevated risk are likely attributable to referral bias. That is, patients with ESCC are more likely to travel far distances to MNH and ORCI for cancer care as compared with individuals with other medical conditions who are appropriate for care at lower-level health facilities. This is evident in the relatively few controls (12%) in the younger group from outside ORCI and MNH's proximate catchment area. However, our study, as well as previous studies, reported a high proportion of ESCC cases occurring in the Northern Lake Zone, even when compared with other regions of similar distance to cancer referral centers.[10,11] These findings, along with the high proportion of young cases from this area, raise important questions about the geographic distribution of the putative risk factors under investigation. Further investigations of behavioral risk factors and environmental exposures in this area are warranted.

The relationship between smoking tobacco and ESCC in Eastern and Southern Africa has been well-established.[17,21,32-35] However, the low prevalence of tobacco use in these regions (men < 20%, women < 3%[36]) casts doubt on the role of tobacco as a solitary ESCC risk factor. In our analysis, we found no association between tobacco use and early-onset disease. This finding is consistent with the previously published Kenyan case series, which found a low prevalence of smoking tobacco (15%) in cases ≤ 30 years.[19] Notably, in our study, secondhand tobacco smoke exposure emerged as a risk factor in the younger group, whereas tobacco smoking emerged as a risk factor in the older group. We speculate that the difference in age-specific effects of tobacco smoking may be due to timing of smoking initiation and the latency of carcinogenic effects. Although tobacco may not be a leading ESCC risk factor in young people in Tanzania, the strong association between tobacco use and ESCC and links with secondhand smoke exposure suggest that tobacco control strategies should be considered as part of prevention efforts.

Although previous research has demonstrated strong links between alcohol consumption and ESCC risk in many settings,[5,31] findings from case-control studies in Eastern and Southern Africa have been mixed.[17,21,32-35,37-40] In our age-stratified analysis, we found no association between alcohol and early-onset disease. Our findings are comparable with the Kenyan case series which found a low prevalence of alcohol consumption (15%) among ESCC cases ≤ 30 years.[19] Few conclusions can be drawn from two studies alone; however, both argue against alcohol as a major risk factor for early-onset disease in Eastern Africa.

Investigation of human papillomavirus (HPV) as a risk factor was not included in the original study[17]; however, links between HPV and ESCC have been previously investigated.[41-43] The InterSCOPE study is one of the most definitive studies to date examining the relationship between ESCC and HPV, with results suggesting that HPV is unlikely to be an important risk factor for ESCC.[44,45]

A summary of the strengths and limitations of our original case-control study was previously published.[17] Major limitations include recruitment from national referral centers, self-report of exposures, exclusion of study participants age ≤ 30 years, and inclusion of patients diagnosed on the basis of clinical criteria. Although > 90% of cases in Tanzania are of squamous cell histology, the inclusion of

adenocarcinoma cases may have attenuated the true relationship between certain risk factors and ESCC. In addition, our findings may be susceptible to selection bias due to geographic differences in residence between cases and controls. This limitation could be addressed in a future study with a multisite recruitment strategy. In our age-stratified analysis, three additional limitations arose. First, the age-matching strategy used at the time of recruitment, whereby controls were matched 1:1 with cases by age ± 10 years, limited our use of matching in age-stratified analyses, hence our use of logistic (unconditional) regression. While conditional logistic regression is more commonly used with matched case-control studies, standard logistic regression has been shown to be an appropriate alternative in this analytic context.[46] Second, because of the few cases of early-onset ESCC, this analysis was limited by the sample size. Pooled analyses of young cases from parallel case-control studies currently underway at Eastern African sites will be needed for more robust analyses. Finally, the comparison of age-specific effects is limited by potential differences in unmeasured confounders between age groups.

In conclusion, the high incidence of ESCC in young people is unique to Eastern Africa. This epidemiologic observation offers an important opportunity to better understand ESCC risk factors. Overall, our findings suggest the presence of not one dominant risk factor, but rather a constellation of risk factors may underlie the high incidence of early-onset disease in Tanzania. These findings require replication, with further study of possible interactions between risk factors. The lack of association between family history of EC and early-onset disease is noteworthy. A multisite genome-wide association study is currently underway, which will provide further insight into the possibility of genetic susceptibility in this patient population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209-249, 2021
2. Arnold M, Ferlay J, van Berge Henegouwen MI, et al: Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut 69:1564-1571, 2020
3. Cheng ML, Zhang L, Borok M, et al: The incidence of oesophageal cancer in Eastern Africa: Identification of a new geographic hot spot? Cancer Epidemiol 39:143-149, 2015
4. Malekzadeh R, Abnet CC, Dawsey SM: Oesophageal cancer: A tale of two malignancies, in Wild CP, Weiderpass E, Stewart BW (eds): World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France, International Agency for Research on Cancer, 2020. http://publications.iarc.fr/586
5. Abnet CC, Arnold M, Wei W-Q: Epidemiology of esophageal squamous cell carcinoma. Gastroenterology 154:360-373, 2018
6. National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER) Program, SEER*stat Database: Incidence—SEER 9 Regs Research Data, Total U.S., 1969-2017 Counties, 2019. www.seer.gov
7. Khazaei S, Ayubi E, Mansori K, et al: Geographic, sex and age distribution of esophageal cancer incidence in Iran: A population-based study. Middle East J Cancer 8:103-108, 2017
8. Zeng H, Zheng R, Zhang S, et al: Esophageal cancer statistics in China, 2011: Estimates based on 177 cancer registries. Thorac Cancer 7:232-237, 2016
9. Chasimpha SJD, Parkin DM, Masamba L, et al: Three-year cancer incidence in Blantyre, Malawi (2008-2010). Int J Cancer 141:694-700, 2017
10. Mmbaga EJ, Deardorff KV, Mushi B, et al: Characteristics of esophageal cancer cases in Tanzania. J Glob Oncol 4:1-10, 2018
11. Gabel JV, Chamberlain RM, Ngoma T, et al: Clinical and epidemiologic variations of esophageal cancer in Tanzania. World J Gastrointest Oncol 8:314-320, 2016
12. Cotton RGH, Langer R, Leong T, et al: Coping with esophageal cancer approaches worldwide. Ann N Y Acad Sci 1325:138-158, 2014
13. Wakhisi J, Patel K, Buziba N, et al: Esophageal cancer in north rift valley of western Kenya. Afr Health Sci 5:157-163, 2005
14. Horner M-J, Salima A, Chilima C, et al: Frequent HIV and young age among individuals with diverse cancers at a national Teaching Hospital in Malawi. J Glob Oncol 4:1-11, 2018
15. Kayamba V, Sinkala E, Mwanamakondo S, et al: Trends in upper gastrointestinal diagnosis over four decades in Lusaka, Zambia: A retrospective analysis of endoscopic findings. BMC Gastroenterol 15:1-9, 2015
16. Parker RK, Dawsey SM, Abnet CC, et al: Frequent occurrence of esophageal cancer in young people in western Kenya. Dis Esophagus 144:724-732, 2008
17. Mmbaga EJ, Mushi BP, Deardorff K, et al: A case-control study to evaluate environmental and lifestyle risk factors for esophageal cancer in Tanzania. Cancer Epidemiol Biomarkers Prev 30:305-316, 2020
18. Smits J, Steendijk R: The International Wealth Index (IWI). Soc Indic Res 122:65-85, 2015
19. Dawsey SP, Tonui S, Parker RK, et al: Esophageal cancer in young people: A case series of 109 cases and review of the literature. PLoS One 5:1-6, 2010
20. Middleton DRS, Menya D, Kigen N, et al: Hot beverages and oesophageal cancer risk in western Kenya: Findings from the ESCCAPE case-control study. Int J Cancer 144:2669-2676, 2019
21. Patel K, Wakhisi J, Mining S, et al: Esophageal cancer, the topmost cancer at MTRH in the Rift Valley, Kenya, and its potential risk factors. ISRN Oncol 2013:503249, 2013
22. Menya D, Maina SK, Kibosia C, et al: Dental fluorosis and oral health in the African esophageal cancer corridor: Findings from the Kenya ESCCAPE case-control study and a pan-African perspective. Int J Cancer 145:99-109, 2018
23. Mmbaga BT, Mwasamwaja A, Mushi G, et al.: Missing and decayed teeth, oral hygiene and dental staining in relation to esophageal cancer risk: ESCCAPE case-control study in Kilimanjaro, Tanzania. Int J Cancer 148:2416-2428, 2020
24. Wei W-Q, Abnet CC, Lu N, et al: Risk factors for oesophageal squamous dysplasia in adult inhabitants of a high risk region of China. Gut 54:759-763, 2005
25. Abnet CC, Qiao YL, Mark SD, et al: Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes Control 12:847-854, 2001
26. Abnet CC, Kamangar F, Islami F, et al: Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 17:3062-3068, 2008
27. Dar NA, Islami F, Bhat GA, et al: Poor oral hygiene and risk of esophageal squamous cell carcinoma in Kashmir. Br J Cancer 109:1367-1372, 2013
28. Chen X, Yuan Z, Lu M, et al: Poor oral health is associated with an increased risk of esophageal squamous cell carcinoma—A population-based case-control study in China. Int J Cancer 140:626-635, 2017
29. Liang H, Yang Z, Wang JB, et al: Association between oral leukoplakia and risk of upper gastrointestinal cancer death: A follow-up study of the Linxian general population Trial. Thorac Cancer 8:642-648, 2017
30. Come J, Pereira JB, Pinto R, et al: The upper digestive tract microbiome and oesophageal squamous cell carcinoma: Epidemiology, pathogenesis, and clinical implications in Africa. Pathobiology 88:141-155, 2021
31. World Cancer Research Fund/American Institute for Cancer Research: Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. Continuous Update Project Expert Report, 2018
32. Kayamba V, Bateman AC, Asombang AW, et al: HIV infection and domestic smoke exposure, but not human papillomavirus, are risk factors for esophageal squamous cell carcinoma in Zambia: A case-control study. Cancer Med 4:588-595, 2015
33. Mlombe YB, Rosenberg NE, Wolf LL, et al: Environmental risk factors for oesophageal cancer in Malawi: A case-control study. Malawi Med J 27:88-92, 2015
34. Sewram V, Sitas F, O'Connell D, et al: Tobacco and alcohol as risk factors for oesophageal cancer in a high incidence area in South Africa. Cancer Epidemiol 41:113-121, 2016
35. Vizcaino AP, Parkin DM, Skinner ME: Risk factors associated with oesophageal cancer in Bulawayo, Zimbabwe. Br J Cancer 72:769-773, 1995
36. McCormack VA, Menya D, Munishi MO, et al: Informing etiologic research priorities for squamous cell esophageal cancer in Africa: A review of setting-specific exposures to known and putative risk factors. Int J Cancer 140:259-271, 2017
37. Segal I, Reinach SG, de Beer M: Factors associated with oesophageal cancer in Soweto, South Africa. Br J Cancer 58:681-686, 1988
38. Pacella-Norman R, Urban MI, Sitas F, et al: Risk factors for oesophageal, lung, oral and laryngeal cancers in black South Africans. Br J Cancer 86:1751-1756, 2002
39. Menya D, Kigen N, Oduor M, et al: Traditional and commercial alcohols and esophageal cancer risk in Kenya. Int J Cancer 144:459-469, 2019
40. Matsha T, Brink L, van Rensburg S, et al: Traditional home-brewed beer consumption and iron status in patients with esophageal cancer and healthy control subjects from Transkei, South Africa. Nutr Cancer 56:67-73, 2006

41. IARC: Human papillomaviruses, in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 90. Geneva, Switzerland, World Health Organization, 2007
42. Rajendra S, Pavey D, McKay O, et al: Human papillomavirus infection in esophageal squamous cell carcinoma and esophageal adenocarcinoma: A concise review. Ann N Y Acad Sci 1482:36-48, 2020
43. Kamangar F, Chow W-H, Abnet C, et al: Environmental causes of esophageal cancer. Gastroenterol Clin North Am 38:27-57, vii, 2009
44. Sitas F, Egger S, Urban M, et al: InterSCOPE study: Associations between esophageal squamous cell carcinoma and human papillomavirus serological markers. J Natl Cancer Inst 104:147-158, 2012
45. Halec G, Schmitt M, Egger S, et al: Mucosal alpha-papillomaviruses are not associated with esophageal squamous cell carcinomas: Lack of mechanistic evidence from South Africa, China and Iran and from a world-wide meta-analysis. Int J Cancer 139:85-98, 2016
46. Pearce N: Analysis of matched case-control studies. BMJ 352:i969, 2016

APPENDIX

TABLE A1. Estimates of the Association of Sociodemographic Characteristics With ESCC Within Each Age Group on the Basis of Univariate Logistic Regression

Sociodemographic Characteristic	Younger Group (age 30-44 years)			Older Group (age ≥ 45 years)		
	Cases (n = 100), No. (%)	Controls (n = 108), No. (%)	OR (95% CI)	Cases (n = 371), No. (%)	Controls (n = 363), No. (%)	OR (95% CI)
Zone						
Coastal-Zanzibar	58 (58)	95 (88)	1	167 (45)	248 (69)	1
Central	7 (7)	4 (4)	2.87 (0.80 to 10.22)	53 (14)	17 (5)	**4.63 (2.59 to 8.27)**
Lake	3 (3)	3 (3)	1.64 (0.32 to 8.39)	19 (5)	31 (9)	0.91 (0.50 to 1.66)
Northern	24 (24)	2 (2)	**19.65 (4.48 to 86.25)**	84 (23)	40 (11)	**3.12 (2.04 to 4.77)**
Southern Highlands	8 (8)	4 (4)	3.28 (0.94 to 11.36)	45 (12)	21 (6)	**3.18 (1.83 to 5.54)**
Unknown				3	6	
Education						
None	8 (8)	3 (3)	1	84 (23)	45 (12)	1
Any primary level	75 (75)	63 (58)	0.45 (0.11 to 1.75)	242 (66)	209 (58)	**0.62 (0.41 to 0.93)**
Any secondary	10 (10)	28 (26)	**0.13 (0.03 to 0.61)**	29 (8)	71 (20)	**0.22 (0.12 to 0.38)**
Postsecondary or above	7 (7)	14 (13)	**0.19 (0.04 to 0.94)**	14 (4)	38 (10)	**0.20 (0.10 to 0.40)**
Unknown				2		
Occupation						
Agriculture	40 (40)	21 (19)	1	210 (57)	121 (33)	1
Business	19 (19)	30 (28)	**0.33 (0.15 to 0.73)**	26 (7)	54 (15)	**0.28 (0.17 to 0.47)**
Office work	3 (3)	13 (12)	**0.12 (0.03 to 0.47)**	29 (8)	48 (13)	**0.35 (0.21 to 0.58)**
Other	38 (38)	44 (41)	**0.45 (0.23 to 0.90)**	106 (29)	139 (38)	**0.44 (0.31 to 0.62)**
Unknown					1	
Household income, TSH						
< 150,000	8 (8)	1 (1)	1	17 (6)	14 (5)	1
150,001-500,000	7 (7)	8 (7)	0.11 (0.01 to 1.11)	48 (17)	27 (9)	1.46 (0.63 to 3.43)
500,001-900,000	16 (16)	15 (14)	0.13 (0.01 to 1.20)	69 (25)	48 (17)	1.18 (0.53 to 2.63)
900,001-1,200,000	17 (17)	13 (12)	0.16 (0.02 to 1.48)	62 (22)	45 (16)	1.13 (0.51 to 2.54)
> 1,200,000	27 (27)	43 (40)	**0.08 (0.01 to 0.66)**	80 (29)	153 (53)	**0.43 (0.20 to 0.92)**
Unknown	25	28		95	76	
IWI[a]						
High (67-100)	24 (25)	48 (45)	1	71 (20)	164 (46)	1
Medium (33 ≤ 67)	42 (43)	40 (37)	**2.1 (1.09 to 4.04)**	126 (35)	95 (27)	**3.06 (2.08 to 4.50)**
Low (0 ≤ 33)	31 (32)	19 (18)	**3.26 (1.54 to 6.92)**	165 (46)	95 (27)	**4.01 (2.76 to 5.84)**
Unknown	3	1		9	9	
Family history of EC						
No	97 (97)	101 (94)	1	338 (93)	351 (99)	1
Yes	3 (3)	7 (6)	0.45 (0.11 to 1.78)	24 (7)	5 (1)	**4.98 (1.88 to 13.21)**
Unknown				9	7	

NOTE. Statistically significant findings are highlighted as bold text.

Abbreviations: EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; IWI, International Wealth Index; OR, odds ratio; TSH, Tanzanian Shillings.

[a]IWI[18] scores range from 0 to 100 (low to high) and are calculated based on nine consumer durables or housing characteristics, including television, refrigerator, telephone, radio, washing machine, toilet, floor material, electricity, and drinking water source.

TABLE A2. Estimates of the Association of Lifestyle Risk Behaviors With ESCC Within Each Age Group on the Basis of Univariate Logistic Regression

	Younger Group (age 30-44 years)			Older Group (age ≥ 45 years)		
Lifestyle Risk Behavior	**Cases (n = 100), No. (%) n = 100**	**Controls (n = 108), No. (%)**	**OR (95% CI)**	**Cases (n = 371), No. (%)**	**Controls (n = 363), No. (%)**	**OR (95% CI)**
Oral health						
How often teeth cleaned						
Daily	89 (89)	105 (97)	1	268 (72)	307 (86)	1
Less than daily	11 (11)	3 (3)	**4.33 (1.17 to 15.99)**	102 (28)	52 (14)	**2.25 (1.55 to 3.26)**
Unknown				1	4	
Experienced loss of teeth						
No	59 (59)	53 (49)	1	90 (24)	113 (31)	1
Yes	40 (40)	55 (51)	0.65 (0.38 to 1.13)	280 (76)	250 (69)	**1.41 (1.02 to 1.95)**
Unknown	1			1		
Smoking status						
Current smoking status						
Never	60 (60)	75 (69)	1	166 (45)	212 (59)	1
Former	21 (21)	17 (16)	1.54 (0.75 to 3.18)	135 (36)	107 (30)	**1.61 (1.16 to 2.23)**
Current	19 (19)	16 (15)	1.48 (0.70 to 3.13)	70 (19)	43 (12)	**2.08 (1.35 to 3.20)**
Unknown					1	
Smoking tobacco (current or former use)						
No	60 (60)	76 (70)	1	171 (46)	217 (60)	1
Yes	40 (40)	32 (30)	1.58 (0.89 to 2.81)	200 (54)	145 (40)	**1.75 (1.31 to 2.35)**
Unknown					1	
Alcohol use						
Current alcohol status						
Never	44 (44)	42 (39)	1	142 (38)	128 (35)	1
Former (last drink > 1 year)	28 (28)	30 (28)	0.89 (0.46 to 1.73)	113 (30)	142 (39)	0.72 (0.51 to 1.01)
Current	28 (28)	36 (33)	0.74 (0.39 to 1.42)	116 (31)	93 (26)	1.12 (0.78 to 1.62)
Home-brewed alcohol (any type; current or former use)						
No	72 (73)	91 (85)	1	189 (51)	249 (69)	1
Yes	26 (27)	16 (15)	**2.05 (1.02 to 4.12**)	180 (49)	114 (31)	**2.08 (1.54 to 2.81)**
Unknown	2	1		2		
Consumption of hot beverages						
How many hot beverages daily						
+1 hot drink daily	—	—	**1.79 (1.11 to 2.91)**			**1.36 (1.04 to 1.77)**
Preferred beverage temperature						
Cold or room temperature	7 (7)	13 (12)	1	50 (13)	48 (13)	1
Hot or very hot	93 (93)	95 (88)	1.82 (0.69 to 4.76)	321 (87)	315 (87)	0.98 (0.64 to 1.50)
No. of times burnt tongue or mouth in the past year						
< 3 times	58 (58)	69 (64)	1	200 (54)	201 (56)	1
3-8 times	32 (32)	30 (28)	1.27 (0.69 to 2.33)	129 (35)	139 (38)	0.93 (0.68 to 1.27)
≥ 9 times	10 (10)	9 (8)	1.32 (0.50 to 3.47)	41 (11)	22 (6)	**1.87 (1.08 to 3.26)**
Unknown				1	1	

(Continued on following page)

TABLE A2. Estimates of the Association of Lifestyle Risk Behaviors With ESCC Within Each Age Group on the Basis of Univariate Logistic Regression (Continued)

	Younger Group (age 30-44 years)			Older Group (age ≥ 45 years)		
Lifestyle Risk Behavior	Cases (n = 100), No. (%) n = 100	Controls (n = 108), No. (%)	OR (95% CI)	Cases (n = 371), No. (%)	Controls (n = 363), No. (%)	OR (95% CI)
Ate soil or clay as a child						
No	80 (80)	95 (88)	1	312 (84)	326 (90)	1
Yes	20 (20)	13 (12)	1.83 (0.86 to 3.90)	59 (16)	37 (10)	**1.67 (1.07 to 2.59)**
Previously worked on a farm						
No	36 (36)	53 (49)	1	59 (16)	121 (33)	1
Yes	64 (64)	55 (51)	1.71 (0.98 to 2.99)	312 (84)	242 (67)	**2.64 (1.86 to 3.77)**
Pesticide exposure						
No	88 (88)	94 (87)	1	298 (80)	305 (84)	1
Yes	12 (12)	14 (13)	0.92 (0.40 to 2.09)	73 (20)	58 (16)	1.29 (0.88 to 1.88)

NOTE. Statistically significant findings are highlighted as bold text.
Abbreviations: ESCC, esophageal squamous cell carcinoma; OR, odds ratio.

TABLE A3. Estimates of the Association of Household Exposures and ESCC Within Each Age Group on the Basis of Univariate Logistic Regression

	Younger Group (age 30-44 years)			Older Group (age ≥ 45 years)		
Household Exposure	**Cases (n = 100), No. (%)**	**Controls (n = 108), No. (%)**	**OR (95% CI)**	**Cases (n = 371), No. (%)**	**Controls (n = 363), No. (%)**	**OR (95% CI)**
Secondhand tobacco smoke in the house						
No	69 (70)	89 (83)	1	259 (71)	284 (79)	1
Yes	30 (30)	18 (17)	**2.15 (1.11 to 4.17)**	106 (29)	76 (21)	**1.53 (1.09 to 2.15)**
Unknown	1	1		6	3	
Cooking site						
Indoors, ventilated	60 (60)	71 (66)	1	166 (45)	180 (50)	1
Indoors, unventilated	4 (4)	1 (1)	4.73 (0.52 to 43.50)	12 (3)	8 (2)	1.63 (0.65 to 4.08)
Outdoors	36 (36)	36 (33)	1.18 (0.67 to 2.10)	191 (52)	174 (48)	1.19 (0.89 to 1.60)
Unknown				2	1	
Firewood cooking in home						
No	41 (41)	66 (61)	1	74 (20)	142 (39)	1
Yes	59 (59)	42 (39)	**2.26 (1.30 to 3.94)**	297 (80)	221 (61)	**2.58 (1.85 to 3.59)**
Slept near a burning fire during childhood						
No	45 (45)	55 (51)	1	110 (30)	140 (39)	1
Yes	55 (55)	53 (49)	1.27 (0.74 to 2.19)	260 (70)	223 (61)	**1.48 (1.09 to 2.02)**
Unknown				1		
Grain/nut preserved						
No	34 (34)	52 (48)	1	59 (16)	116 (32)	1
Yes	66 (66)	56 (52)	**1.80 (1.03 to 3.16)**	312 (84)	247 (68)	**2.48 (1.74 to 3.54)**
Grain/nut has been infected by pests						
No	67 (69)	91 (86)	1	259 (71)	284 (81)	1
Yes	30 (31)	15 (14)	**2.72 (1.35 to 5.44)**	104 (29)	66 (19)	**1.73 (1.22 to 2.46)**
Unknown	3	2		8	13	
Water source						
Borehole or well	27 (27)	22 (20)	1	114 (31)	100 (28)	1
Water from spring	0 (0)	1 (1)	—	0	3 (1)	—
Rain water or surface water	1 (1)	2 (2)	0.41 (0.03 to 4.80)	16 (4)	6 (2)	2.34 (0.88 to 6.21)
Piped water in house or bottled water	71 (72)	83 (77)	0.70 (0.37 to 1.33)	241 (65)	253 (70)	0.84 (0.61 to 1.15)
Unknown	1				1	

NOTE. Statistically significant findings are highlighted as bold text.

Abbreviations: ESCC, esophageal squamous cell carcinoma; OR, odds ratio.

TABLE A4. Estimates of the Association of Self-Reported Food Frequency and ESCC Within Each Age Group on the Basis of Univariate Logistic Regression

	Younger Group (age 30-44 years)			Older Group (age ≥ 45 years)		
Frequency of Consumption	**Cases (n = 100), No. (%)**	**Controls (n = 108), No. (%)**	**OR (95% CI)**	**Cases (n = 371), No. (%)**	**Controls (n = 363), No. (%)**	**OR (95% CI)**
Rice						
< 1 time per week	32 (32)	23 (21)	1	152 (41)	117 (32)	1
1-2 times/wk	23 (23)	35 (33)	0.47 (0.22 to 1.00)	132 (36)	131 (36)	0.78 (0.55 to 1.09)
3-5 times/wk	37 (37)	38 (36)	0.70 (0.35 to 1.41)	78 (21)	76 (21)	0.79 (0.53 to 1.18)
Daily	8 (8)	11 (10)	0.52 (0.18 to 1.50)	9 (2)	37 (10)	**0.19 (0.09 to 0.40)**
Unknown		1			2	
Wheat/bread/pasta						
< 1 time per week	29 (29)	27 (25)	1	176 (47)	196 (54)	1
1-2 times/wk	29 (29)	27 (25)	1.00 (0.48 to 2.10)	94 (25)	64 (18)	**1.64 (1.12 to 2.39)**
3-5 times/wk	36 (36)	40 (37)	0.84 (0.42 to 1.67)	92 (25)	83 (23)	1.23 (0.86 to 1.77)
Daily	6 (6)	13 (12)	0.43 (0.14 to 1.29)	9 (2)	20 (6)	0.50 (0.22 to 1.13)
Unknown		1				
Chipsi (fried potato)						
< 1 time per week	51 (51)	46 (43)	1	266 (72)	240 (66)	1
1-2 times/wk	23 (23)	32 (30)	0.65 (0.33 to 1.26)	65 (18)	80 (22)	0.73 (0.51 to 1.06)
3-5 times/wk	20 (20)	17 (16)	1.06 (0.50 to 2.27)	25 (7)	22 (6)	1.03 (0.56 to 1.87)
Daily	6 (6)	12 (11)	0.45 (0.16 to 1.30)	15 (4)	19 (5)	0.71 (0.35 to 1.43)
Unknown		1			2	
Beans						
< 1 time per week	9 (9)	6 (6)	1	22 (6)	24 (7)	1
1-2 times/wk	8 (8)	4 (4)	1.33 (0.27 to 6.50)	20 (5)	25 (7)	0.87 (0.38 to 1.99)
3-5 times/wk	28 (28)	38 (36)	0.49 (0.16 to 1.54)	90 (24)	106 (29)	0.93 (0.49 to 1.76)
Daily	55 (55)	59 (55)	0.62 (0.21 to 1.86)	239 (64)	205 (57)	1.27 (0.69 to 2.34)
Unknown		1			3	
Cooked greens						
< 1 time per week	12 (12)	10 (9)	1	43 (12)	55 (15)	1
1-2 times/wk	19 (19)	17 (16)	0.93 (0.32 to 2.70)	81 (22)	81 (22)	1.28 (0.77 to 2.12)
3-5 times/wk	30 (30)	26 (24)	0.96 (0.36 to 2.59)	134 (36)	91 (25)	**1.88 (1.17 to 3.04)**
Daily	39 (39)	54 (50)	0.60 (0.24 to 1.53)	113 (30)	135 (37)	1.07 (0.67 to 1.71)
Unknown		1			1	
Raw greens						
< 1 time per week	40 (40)	27 (25)	1	152 (41)	106 (29)	1
1-2 times/wk	43 (43)	53 (49)	0.55 (0.29 to 1.03)	143 (39)	143 (40)	**0.70 (0.50 to 0.98)**
3-5 times/wk	13 (13)	13 (12)	0.68 (0.27 to 1.68)	55 (15)	68 (19)	**0.56 (0.37 to 0.87)**
Daily	4 (4)	15 (14)	**0.18 (0.05 to 0.60)**	21 (6)	44 (12)	**0.33 (0.19 to 0.59)**
Unknown					2	

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TABLE A4. Estimates of the Association of Self-Reported Food Frequency and ESCC Within Each Age Group on the Basis of Univariate Logistic Regression (Continued)

	Younger Group (age 30-44 years)			Older Group (age ≥ 45 years)		
Frequency of Consumption	**Cases (n = 100), No. (%)**	**Controls (n = 108), No. (%)**	**OR (95% CI)**	**Cases (n = 371), No. (%)**	**Controls (n = 363), No. (%)**	**OR (95% CI)**
Pickled vegetables						
< 1 time per week	53 (53)	64 (59)	1	210 (57)	196 (54)	1
1-2 times/wk	32 (32)	26 (24)	1.49 (0.79 to 2.80)	100 (27)	96 (27)	0.97 (0.69 to 1.37)
3-5 times/wk	10 (10)	7 (6)	1.73 (0.61 to 4.84)	40 (11)	42 (12)	0.89 (0.55 to 1.43)
Daily	5 (5)	11 (10)	0.55 (0.18 to 1.68)	20 (5)	28 (8)	0.67 (0.36 to 1.22)
Unknown				1	1	
Fruit						
< 1 time per week	14 (14)	14 (13)	1	63 (17)	62 (17)	1
1-2 times/wk	27 (27)	21 (20)	1.29 (0.50 to 3.27)	97 (26)	94 (26)	1.02 (0.65 to 1.59)
3-5 times/wk	40 (40)	31 (29)	1.29 (0.54 to 3.10)	150 (41)	87 (24)	**1.70 (1.09 to 2.63)**
Daily	19 (19)	40 (38)	0.48 (0.19 to 1.19)	60 (16)	119 (33)	**0.50 (0.31 to 0.79)**
Unknown		2		1	1	
Smoked fish						
< 1 time per week	23 (23)	25 (23)	1	94 (25)	92 (25)	1
1-2 times/wk	38 (38)	27 (25)	1.53 (0.72 to 3.24)	118 (32)	112 (31)	1.03 (0.70 to 1.52)
3-5 times/wk	33 (33)	44 (41)	0.82 (0.40 to 1.68)	142 (38)	106 (29)	1.31 (0.89 to 1.92)
Daily	6 (6)	11 (10)	0.59 (0.19 to 1.86)	16 (4)	53 (15)	**0.30 (0.16 to 0.55)**
Unknown		1		1		
Smoked meat						
< 1 time per week	53 (53)	46 (43)	1	194 (52)	158 (44)	1
1-2 times/wk	30 (30)	37 (35)	0.70 (0.38 to 1.31)	112 (30)	138 (38)	**0.66 (0.48 to 0.92)**
3-5 times/wk	16 (16)	19 (18)	0.73 (0.34 to 1.58)	55 (15)	59 (16)	0.76 (0.50 to 1.16)
Daily	1 (1)	5 (5)	0.17 (0.02 to 1.54)	10 (3)	8 (2)	1.02 (0.39 to 2.64)
Unknown		1				
Stewed/boiled meat						
< 1 time per week	14 (14)	15 (14)	1	78 (21)	68 (19)	1
1-2 times/wk	47 (48)	32 (30)	1.57 (0.67 to 3.70)	134 (36)	143 (40)	0.82 (0.55 to 1.22)
3-5 times/wk	35 (36)	54 (50)	0.69 (0.30 to 1.61)	138 (37)	129 (36)	0.93 (0.62 to 1.40)
Daily	2 (2)	6 (6)	0.36 (0.06 to 2.07)	20 (5)	19 (5)	0.92 (0.45 to 1.86)
Unknown	2	1		1	4	
Milk						
Never	5 (5)	2 (2)	1	10 (3)	11 (3)	1
< 1 time per week	47 (48)	50 (49)	0.38 (0.07 to 2.03)	197 (56)	194 (57)	1.12 (0.46 to 2.69)
1-2 times/wk	29 (30)	27 (26)	0.43 (0.08 to 2.40)	91 (26)	72 (21)	1.39 (0.56 to 3.46)
3-5 times/wk	16 (16)	23 (23)	0.28 (0.05 to 1.62)	56 (16)	61 (18)	1.01 (0.40 to 2.56)
Daily	2 (2)	6 (6)	0.13 (0.01 to 1.32)	12 (3)	19 (5)	0.69 (0.23 to 2.13)
Unknown	1			5	6	

(Continued on following page)

TABLE A4. Estimates of the Association of Self-Reported Food Frequency and ESCC Within Each Age Group on the Basis of Univariate Logistic Regression (Continued)

Frequency of Consumption	Younger Group (age 30-44 years)			Older Group (age ≥ 45 years)		
	Cases (n = 100), No. (%)	Controls (n = 108), No. (%)	OR (95% CI)	Cases (n = 371), No. (%)	Controls (n = 363), No. (%)	OR (95% CI)
Spicy chilies						
< 1 time per week	33 (33)	42 (39)	1	119 (32)	137 (38)	1
1-2 times/wk	12 (12)	15 (14)	1.02 (0.42 to 2.47)	43 (12)	59 (16)	0.84 (0.53 to 1.33)
3-5 times/wk	25 (25)	18 (17)	1.77 (0.83 to 3.77)	92 (25)	103 (28)	1.03 (0.71 to 1.49)
Daily	30 (30)	33 (31)	1.16 (0.59 to 2.27)	117 (32)	64 (18)	**2.10 (1.42 to 3.11)**
Unknown						
Maize meal						
< 1 time per week	1 (1)	0 (0)	NC	8 (2)	10 (3)	1
1-2 times/wk	4 (4)	4 (4)	NC	10 (3)	15 (4)	0.83 (0.24 to 2.84)
3-5 times/wk	28 (28)	33 (31)	NC	76 (20)	82 (23)	1.16 (0.43 to 3.09)
Daily	67 (67)	70 (65)	NC	277 (75)	256 (71)	1.35 (0.53 to 3.48)
Unknown		1				
Cassava						
< 1 time per week	38 (38)	36 (34)	1	158 (43)	164 (45)	1
1-2 times/wk	25 (25)	18 (17)	1.32 (0.62 to 2.81)	77 (21)	78 (22)	1.02 (0.70 to 1.50)
3-5 times/wk	25 (25)	39 (36)	0.61 (0.31 to 1.20)	89 (24)	70 (19)	1.32 (0.90 to 1.93)
Daily	12 (12)	14 (13)	0.81 (0.33 to 1.99)	47 (13)	49 (14)	1.00 (0.63 to 1.57)
Unknown		1			2	
Groundnuts/ peanuts						
< 1 time per week	43 (43)	53 (50)	1	158 (43)	161 (45)	1
1-2 times/wk	43 (43)	39 (36)	1.36 (0.75 to 2.45)	149 (40)	151 (42)	1.01 (0.73 to 1.38)
3-5 times/wk	10 (10)	10 (9)	1.23 (0.47 to 3.23)	51 (14)	38 (11)	1.37 (0.85 to 2.20)
Daily	4 (4)	5 (5)	0.99 (0.25 to 3.90)	13 (4)	11 (3)	1.20 (0.52 to 2.77)
Unknown		1			2	
Salted foods						
< 1 time per week	3 (3)	7 (7)	1	16 (4)	24 (7)	1
1-2 times/wk	1 (1)	2 (2)	1.17 (0.07 to 18.35)	11 (3)	12 (3)	1.37 (0.49 to 3.87)
3-5 times/wk	6 (6)	2 (2)	7.00 (0.86 to 56.89)	13 (4)	36 (10)	0.54 (0.22 to 1.33)
Daily	90 (90)	96 (90)	2.19 (0.55 to 8.72)	331 (89)	290 (80)	1.71 (0.89 to 3.29)
Unknown		1			1	

NOTE. Statistically significant findings are highlighted as bold text.

Abbreviations: ESCC, esophageal squamous cell carcinoma; NC, not calculable; OR, odds ratio.

