A Case–Control Study to Evaluate Environmental and Lifestyle Risk Factors for Esophageal Cancer in Tanzania

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ABSTRACT

Background: East Africa is affected by a disproportionately high burden of esophageal squamous cell carcinoma (ESCC).

Methods: We conducted an incident case–control study in Dar es Salaam, Tanzania with 1:1 matching for gender and age. A questionnaire evaluated known and putative risk factors for ESCC. Cochran–Mantel–Haenszel and multivariable conditional logistic regression analyses were applied to evaluate associations with ESCC risk, with adjustment for geographic zone.

Results: Of 471 cases and 471 controls, the majority were male (69%); median ages were 59 and 55, respectively. In a multivariable logistic regression model, a low International Wealth Index (IWI) score [OR 2.57; 95% confidence interval (CI), 1.41–4.68], former smoking (OR 2.45; 95% CI, 1.46–4.13), second-hand smoke in the household (OR 1.67; 95% CI, 1.01–2.77), daily spicy chilies (OR 1.62; 1.04–2.52), and daily salted foods (OR 2.02; 95% CI, 1.06–3.85) were associated with increased risk of ESCC. Daily consumption of raw greens (OR 0.36; 95% CI, 0.16–0.80), fruit (OR 0.47; 95% CI, 0.27–0.82), and smoked fish (OR 0.31; 95% CI, 0.15–0.66) were protective. Permanent residence in the Central (OR 5.03; 95% CI, 2.16–11.73), Northern-Lake (OR 2.40; 95% CI, 1.46–3.94), or Southern Highlands zones (OR 3.18; 95% CI, 1.56–6.50) of Tanzania were associated with increased risk compared with residence in the Eastern zone.

Conclusions: Low IWI score, smoke exposure(s), geographic zone, and dietary factors were associated with risk for ESCC in Tanzania.

Impact: These findings will inform the development of future hypothesis-driven studies to examine risk factors for the high burden of ESCC in East Africa.

See related commentary by McCormack et al., p. 248

Introduction

Esophageal cancer is the seventh most common cancer and the sixth most common cause of cancer-related death worldwide (1). While esophageal adenocarcinoma is the dominant histologic subtype of esophageal cancer in the developed world, esophageal squamous cell carcinoma (ESCC) is the dominant subtype in low-income countries. The incidence of ESCC is characterized by remarkable variations in geographic distribution, with sharply defined, high-incidence areas in China, India, South-East Asia, and Central Asia (2). Although early reports of the high incidence of esophageal cancer in Africa date back to 1969 (3), East Africa has only recently gained increasing attention as a high-incidence region (4–8). The age-standardized incidence rate of esophageal cancer in East Africa is reported as 8.3 per 100,000 population (9). A unique feature of this high-incidence corridor is that approximately 20% of cases occur in patients younger than 40 years (5–8). The high incidence of ESCC in young people, as well as the geographic distribution along the eastern corridor of Africa, suggest plausible etiologic role(s) for unique environmental, infectious, and/or genetic factors.

ESCC cases in high-income countries are predominantly associated with smoking, alcohol consumption, and low consumption of fruits and vegetables (10). While etiologic and genetic studies of ESCC in Asian populations have been extensive (11), research to understand risk factors for this disease in sub-Saharan Africa is nascent. Available studies speculate on possible contributions to the high incidence in East Africa from thermal damage due to consumption of hot beverages, alcohol, low dietary fruit intake, poor oral hygiene, lower socioeconomic status (SES), low soil selenium levels, mycotoxins, indoor air pollution from biomass burning and other environmental exposures, or possible infectious causes (12–20).

The etiologic heterogeneity for ESCC in other settings underscores the importance of conducting studies in various geographic subpopulations as an effort to identify possibly unique risk factors. We aimed to evaluate risk factors contributing to the high incidence of ESCC in Tanzania.

Materials and Methods

Study design and setting

We conducted an incident case–control study with 1:1 matching for gender and age to evaluate the potential dietary, lifestyle, and environmental risk factors for ESCC in Tanzania. This study was conducted at Muhimbili National Hospital (MNH) and Ocean Road Cancer Institute (ORCI) in Dar es Salaam. Both MNH and ORCI are national referral hospitals that receive a high volume of patients with cancer from throughout Tanzania. Within Dar es Salaam, MNH is the public teaching hospital affiliated with Muhimbili University of Health and Allied Sciences (MUHAS) and provides diagnostic and surgical care for patients with cancer. Cancer cases warranting chemotherapy or radiotherapy are typically referred, following diagnosis, to ORCI,

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Prior presentation: Preliminary data from this study were presented an an oral presentation at the 2016 NCI/CUGH Symposium on Global Cancer Research in San Francisco, CA.

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Cancer Epidemiol Biomarkers Prev 2021;30:305–16

doi: 10.1158/1055-9965.EPI-20-0660

which is the largest cancer center in Tanzania. Because MNH employs a majority of pathologists in Tanzania, patients with medical conditions that require pathologic evaluation, including cancer, may be more likely to be referred from zonal, regional, and district hospitals. Geographic distance, particularly for rural populations, remains a significant barrier to care in Tanzania (21).

The study was approved by institutional review boards at MUHAS (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 prior to enrollment in Swahili, the national language of Tanzania.

Study population

We identified consecutive cases of confirmed or suspected ESCC from medical and surgical wards at MNH between 2013 and 2015. In addition, patients who were actively undergoing treatment for ESCC at ORCI were recruited to participate. Because newly diagnosed cases of ESCC are susceptible to clinical deterioration in this setting, we employed rapid case ascertainment strategies to identify all new diagnoses of ESCC at these institutions. Nonpermanent residents of Tanzania and patients <30 years old were excluded. Because not all Tanzanian patients with a suspected diagnosis of ESCC undergo diagnostic biopsies for pathologic confirmation of malignancy due to prohibitive expense, cases were identified based upon either pathologic confirmation or clinical diagnosis. A clinical diagnosis was defined as findings consistent with ESCC based on CT scan, barium swallow study, or direct tumor visualization via esophagogastroduodenoscopy. We have previously reported >90% pretest probability that a clinical diagnosis using these criteria corresponds to a pathologic diagnosis of ESCC in this setting (22).

Controls were inpatients on the medical, surgical, trauma, and gynecology wards at MNH who were receiving care for nonmalignant conditions. Potential controls were recruited consecutively and matched 1:1 for gender and age ($\pm$10 years). Admissions logbooks were reviewed to identify potentially eligible controls to match the gender and age of already recruited cases. Patients with a history of malignancy or conditions associated with increased risk of esophageal cancer, including GERD and Barrett esophagus, were excluded.

We initially aimed to recruit a sample size of 150 cases and 150 controls; however, due to the rapidity of accrual, the protocol was amended for an enhanced sample size of 473 cases and 473 controls, enabling 80% power to detect ORs>1.5 for exposures with 25% prevalence.

Data collection

We developed a structured questionnaire based upon a comprehensive list of previously reported risk factors for ESCC, as well as other putative risk factors that we hypothesized might be setting specific in Tanzania. We used validated questions from the Tanzania Demographic and Health Survey and Malaria Indicator Survey (23), coupled with *de novo* questions developed for exposures of interest. Both cases and controls participated in face-to-face interviews with one of two research assistants trained for consistency in administration of the questionnaire. All interviews were conducted in Swahili. A family surrogate was allowed to perform the interview on behalf of cases who were unable to speak. Surrogate participation was not allowed for controls. Deidentified data were entered into Research Electronic Data Capture (REDCap), a secure web-based application for data storage.

The first section of the questionnaire collected data from participants on: demographics; residential history; education; income; occupational history, with details about agricultural, animal, and pesticide exposures; medical history; and any family history of esophageal cancer. A lifetime residential and occupational history were obtained; the participant's most recent residence and occupation were used for the current analysis. Annual household income was classified as a categorical variable: >1,200,000 Tanzanian shillings (TZS); 900,001–1,200,000 TZS; 500,001–900,000 TZS; or ≤500,000 TZS.

Data were collected for a variety of behaviors, including: tobacco and alcohol use, oral hygiene, hot beverage consumption, and household exposures. A detailed history of tobacco and alcohol use was obtained, with capture of data on specific type, ages of initiation and cessation, and quantity consumed. Oral health was evaluated by frequency of cleaning, implement used, and any prior history of tooth loss. Hot beverage consumption was evaluated with questions regarding preferred beverage temperature, frequency of consumption, speed of drinking, and occurrences of a burnt tongue within the prior year. Household exposures were evaluated with questions regarding cooking oils used for food preparation, cooking oil reuse, preservation of grains and nuts (yes vs. no, method, and pest infestation), primary location of cooking (inside vs. outside the home, presence of ventilation), and water source.

A food frequency questionnaire evaluated the consumption of: rice, maize (commonly used for *ugali*), wheat, fruits, cassava, fried potatoes (*chipsi*), fresh and cooked vegetables, pickled vegetables, spicy chilies, nuts, smoked fish, preserved and unpreserved meats, and types of milk. The questionnaire included questions regarding common local foods that are often contaminated with fumonisins, a cancer-initiating agent in experimental animals that commonly contaminates maize products. Frequency of consumption was recorded as daily, 3–5 times per week (3–5×/week), 1–2 times per week (1–2×/week), or less often (<1×/week). In the multivariable model, food frequency was categorized as daily or less than daily due to the sparsity in multiple frequency categories.

We defined a composite variable for SES using the International Wealth Index (IWI), which has been previously determined to be a reliable and valid asset-based index of the economic status of a household in any low- and middle-income countries (LMIC) (24). Scores were calculated in the range from 0 to 100 (lowest to highest) for each study participant based on nine consumer durables or household characteristics: television, refrigerator, telephone, radio, washing machine, toilet, floor material, electricity, and drinking water source. The IWI scores were divided into tertiles: low (0–<33), medium (≥33–<66), and high (≥66–100).

Statistical analyses

Cochran—Mantel–Haenszel testing, stratified by the case–control pair, was used to identify risk factors for ESCC in a univariate analysis, which provided estimates of the OR and 95% confidence intervals (CI). In addition, we applied a linear trend test to explore whether food exposures were monotonically associated with ESCC.

To account for possible confounding effect of geographic zone, we also calculated region-adjusted OR (adj OR) and 95% CI for each variable by a conditional logistic model which included the corresponding variable plus region. For this purpose, permanent residences were aggregated into four zones within Tanzania, based upon shared geographic features: (i) "Eastern" comprised of the Coastal zone and Zanzibar, (ii) "Northern-Lake" comprised of the Northern and Lake zones, (iii) "Southern Highlands," and (iv) "Central."

To account for possible confounders and assess the independent effects of the risk factors, multivariable conditional logistic regression modeling was applied (25). Backward-stepwise variable selection

based on Akaike information criterion was subsequently carried out to obtain the final multivariable conditional logistic regression model. In effort to reduce the bias of the estimates of the risk factors associated with ESCC, the final model retained known and putative setting-specific risk factors (12, 17) as well as novel variables from our dataset which remained independently statistically significant at the 5% confidence level following adjustment by the other variables in the multivariable model. To address potential concerns regarding the inclusion of cases based upon a clinical diagnosis alone, we performed a sensitivity analysis which included only the subset of matched case–control pairs with pathologically confirmed cases.

Statistical significance was declared at $P < 0.05$. Multiple testing adjustment was performed by Bonferroni correction within the same category of variables. All analyses were performed using the R statistical computing software (http://www.r-project.org).

Results

Study population

A total of 473 matched case–control pairs were recruited; however, two pairs were excluded from the final dataset due to mismatched gender. A total of 471 matched case–control pairs were analyzed. The median age of cases was 59 years [interquartile range (IQR) 47–69], and the median age of controls was 55 years (IQR 45–65). The majority of cases and controls were male (69%), and nearly all were of African ethnicity. Of the cases, 209 (44%) were pathologically confirmed, and 262 (56%) were diagnosed based upon clinical findings.

The demographic, clinical, and socioeconomic factors of cases and controls are summarized in **Table 1**. Cases were more likely to report a permanent residence outside the Eastern zone of Tanzania than controls (52% vs. 26%, $P < 0.001$). Cases were more likely to report a family history of esophageal cancer (OR 2.50; 95% CI, 1.20–5.21) and less likely to report a history of malaria than controls (OR 0.48; 95% CI, 0.31–0.74). Cases were more likely to have an IWI score in the lowest tertile (42% vs. 24%, $P < 0.001$), and were more likely to report an occupation in agriculture (53% vs. 30%, $P < 0.001$). The associations of several consumer durables or household characteristics, which were collected as indicators of SES, are summarized in Supplementary Table S1; all indicators of lower SES were associated with increased risk for ESCC before and after adjustment for geographic region. HIV status was not associated with increased risk; however, their HIV status was unknown for a large number of participants in both the case and control groups (43% and 36%, respectively).

Univariate analysis

Univariate analyses of behavioral risk factors and lifestyle exposures are presented in **Table 2**. Current smoking (OR 2.1; 95% CI, 1.23–3.58), former smoking (OR 1.93; 95% CI, 1.33–2.80), second-hand smoke exposure (OR 1.78; 95% CI, 1.28–2.48), and a history of sleeping near a fire as a child (OR 1.49; 95% CI, 1.12–1.97) were associated with an increased risk of ESCC. Prior farmwork exposure (OR 2.46; 95% CI, 1.80–3.38), consumption of soil or clay as a child (OR 1.73; 95% CI, 1.17–2.55), preservation of grain/nuts (OR 2.27; 95% CI, 1.67, 3.08), and use of firewood as cooking fuel (OR 2.75; 95% CI, 2.01–3.77) were all associated with increased risk of ESCC. Self-report of daily teeth cleaning was protective against ESCC (OR 0.38; 95% CI, 0.26–0.56), compared with less frequent cleaning. These associations were all corroborated in the conditional logistic regression model adjusted for region.

In univariate analyses of the association of self-reported food intake with ESCC which compared daily versus <1×/week (**Table 3**), the strongest protective effects against ESCC were detected with daily consumption of rice (OR 0.15; 95% CI, 0.03–0.68), raw greens (OR 0.22; 95% CI, 0.08–0.57), fruit (OR 0.50; 95% CI, 0.21–1.17), and smoked fish (OR 0.08; 95% CI, 0.01–0.59). Increased risk of ESCC with daily consumption of spicy chilies (OR 2.22; 95% CI, 1.36–3.63) was detected.

Multivariable conditional logistic regression analysis

The final list of variables included in the multivariable model included: family history of esophageal cancer (yes vs. no), a personal history of malaria (yes vs. no), zone of permanent residence in Tanzania (Eastern vs. Central vs. Northern-Lake vs. Southern Highlands), IWI tertile (high, medium, low), tobacco use (never vs. former vs. current), exposure to second-hand smoke in the home (yes vs. no), cooking location (outdoors vs. indoors ventilated vs. indoors unventilated), use of firewood as cooking fuel (yes vs. no), a history of sleeping by a fire as a child (yes vs. no), alcohol use (never vs. former vs. current), a history of a burnt tongue or mouth due to a hot beverage in the past year (yes vs. no), frequency of teeth cleaning (daily vs. less than daily). Food items that were statistically significant in the univariate model were also included: raw greens, fruit, smoked fish, spicy chilies, and salted foods (daily vs. less than daily).

Results of the multivariable conditional logistic regression analysis for the independent associations of risk factors for ESCC are presented in **Fig. 1**. A permanent residence in the Central zone (OR 5.03; 95% CI, 2.16–11.73), Northern-Lake zone (OR 2.40; 95% CI, 1.46–3.94), or Southern Highlands zone (OR 3.18; 95% CI, 1.56–6.50) of Tanzania were associated with significantly increased risk for ESCC, compared with residence in the Eastern zone. An IWI score in the lowest tertile (OR 2.57; 95% CI, 1.41–4.68) or the middle tertile (OR 2.33; 95% CI, 1.39–3.91) were associated with increased risk with ESCC, when compared with an IWI score in the highest tertile.

Self-reported status as a former smoker was associated with a significantly increased risk (OR 2.45; 95% CI, 1.46–4.13), compared with status as a never-smoker. Status as a current smoker trended toward increased risk (OR 1.54; 95% CI, 0.81–2.93). Exposure to a smoker in the household was associated with increased risk (OR 1.67; 95% CI, 1.01–2.77). Residence in a household with an unventilated indoor cooking location (OR 1.88; 95% CI, 0.47–7.50) or use of firewood as cooking fuel (OR 1.31; 95% CI, 0.80–2.15) both showed suggestion of increased risk but did not achieve statistical significance. Daily teeth cleaning showed suggestion of a protective effect against ESCC, compared with less frequent cleaning (OR 0.61; 95% CI, 0.34–1.08).

Daily consumption of spicy chilies (OR 1.62; 95% CI, 1.04–2.52) and salted foods (OR 2.02; 95% CI, 1.06–3.85) were associated with increased risk of ESCC, compared with less frequent consumption. On the other hand, daily consumption of fruits (OR 0.47; 95% CI, 0.27–0.82), raw greens (OR 0.36; 95% CI, 0.16–0.80), and smoked fish (OR 0.31; 95% CI, 0.15–0.66) were each associated with decreased risk of ESCC, compared with less frequent consumption. To evaluate associations between IWI and the five foods included in the final multivariable model, we used Pearson χ^2 tests on the four levels of food frequency and three tertiles of IWI scores. Consumption of raw greens and salted foods was not statistically associated with IWI. However, the tertile with the highest IWI consumed more fruits ($P < 0.0001$), more smoked fish ($P = 0.001$), and fewer spicy chilies ($P < 0.0001$) compared with the lower IWI tertiles.

Table 1. The associations of demographic, clinical, and socioeconomic factors with esophageal cancer.

	471 Cases *N* (%)	471 Controls *N* (%)	OR[a] (95% CI)	*P*[b]	adj OR[c] (95% CI)	P_{adj}[d]
Age group						
30–39	53 (11.3)	63 (13.4)	NA			
40–49	92 (19.5)	94 (20.0)				
50–59	99 (21.0)	128 (27.2)				
60–69	115 (24.4)	100 (21.2)				
70–79	77 (16.3)	67 (14.2)				
80–89	33 (7.0)	19 (4.0)				
≥90	2 (<1)	0				
Gender						
Male	324 (68.8)	324 (68.8)	NA			
Female	147 (31.2)	147 (31.2)				
Ethnicity						
Arab	0	2 (100)	NC	NC	NC	NC
Caucasian	2 (100)	0				
African	469 (<1)	469 (<1)				
Geographical zone				<0.001	NA	NA
Central	60 (12.7)	21 (4.5)	5.50 (2.59–11.68)			
Lake	22 (4.7)	34 (7.2)	0.57 (0.28–1.16)			
Northern	108 (22.9)	42 (8.9)	4.71 (2.79–7.94)			
Southern Highlands	53 (11.3)	25 (5.3)	3.36 (1.72–6.59)			
Zanzibar	7 (1.5)	10 (2.1)	1.00 (0.32–3.10)			
Coastal	218 (46.3)	333 (70.7)	1			
Unknown	3 (<1)	6 (1.3)				
Family history of esophageal cancer				0.018		0.033
Yes	27 (5.7)	12 (2.5)	2.50 (1.20–5.21)		2.30 (1.04–5.08)	
No	435 (92.4)	452 (96.0)	1		1	
Unknown	9 (1.9)	7 (1.5)				
HIV status				0.322		0.423
Positive	44 (9.3)	65 (13.8)	0.72 (0.41–1.27)		0.78 (0.43–1.43)	
Negative	223 (47.3)	239 (50.7)	1		1	
Unknown	204 (43.3)	167 (35.5)				
History of malaria				<0.001		<0.001
Yes	400 (84.9)	433 (91.9)	0.48 (0.31–0.74)		0.44 (0.27–0.70)	
No	69 (14.6)	36 (7.6)	1		1	
Unknown	2 (<1)	2 (<1)				
Occupation				<0.001		<0.001
Business	45 (9.6)	84 (17.8)	0.30 (0.16–0.54)		0.34 (0.22–0.54)	
Office work	32 (6.8)	61 (13.0)	0.38 (0.19–0.76)		0.38 (0.22–0.66)	
Other	144 (30.6)	183 (38.9)	0.37 (0.25–0.55)		0.53 (0.37–0.77)	
Agriculture	250 (53.1)	142 (30.1)	1		1	
Unknown	0	1 (<1)				
International Wealth Index score[e]				<0.001		<0.001
High (67–100)	95 (20.2)	212 (45.0)	0.23 (0.14–0.38)		0.25 (0.17–0.39)	
Medium (33–<67)	168 (35.7)	135 (28.7)	0.71 (0.48–1.04)		0.76 (0.53–1.10)	
Low (0–<33)	196 (41.6)	114 (24.2)	1		1	
Unknown	12 (2.5)	10 (2.1)				

Note: ORs were not calculated for age or gender because these are matching variables.
Abbreviations: NA, not applicable; NC, not calculable.
[a]Unadjusted OR and its 95% CI calculated on the basis of Cochran—Mantel–Haenszel method stratified by matched case–control pair.
[b]*P* value of unadjusted association test by Cochran–Mantel–Haenszel test. Comparisons do not reflect the unknown groups.
[c]adj OR and its 95% CI based on conditional logistic regression model stratified by matched case–control pair.
[d]*P* value of region-adjusted association test (adj *P* value) by likelihood ratio test using the conditional logistic regression model. Comparisons do not reflect the unknown groups.
[e]IWI scores range from 0 to 100 (low to high) and are calculated on the basis of nine consumer durables or housing characteristics, including: television, refrigerator, telephone, radio, washing machine, toilet, floor material, electricity, and drinking water source.

Sensitivity analyses

The adj OR for each variable are presented in **Tables 1**, **2**, **3** and Supplementary Table S1. In the sensitivity analysis of the subset of matched case–control pairs with pathologically confirmed cases ($n = 209$), all variables maintained the protective or deleterious directions seen with the full dataset but statistical significance was attenuated with the reduced sample size (Supplementary Fig. S1). Despite the reduced sample size in the sensitivity analysis, the lowest IWI tertile retained a statistically significant association with increased risk of ESCC (OR 3.38; 95% CI, 1.23–9.27).

Table 2. The associations of behavioral risk factors and lifestyle exposures with esophageal cancer.

	471 Cases *N* (%)	471 Controls *N* (%)	OR[a] (95% CI)	*P*[b]	adj OR[c] (95% CI)	P_{adj}[d]
Smoking status[f]				<0.001[e]		<0.001[e]
Current	89 (18.9)	59 (12.5)	2.10 (1.23–3.58)		2.23 (1.42–3.51)	
Former[f]	156 (33.1)	124 (26.3)	1.93 (1.33–2.80)		1.84 (1.28–2.65)	
Never	226 (48.0)	287 (60.9)	1		1	
Unknown	0	1 (<1)				
Second-hand smoke in home				<0.001[e]		<0.001 [e]
Yes	136 (28.9)	94 (20.0)	1.78 (1.28–2.48)		1.87 (1.31–2.69)	
No	328 (69.6)	373 (79.2)	1		1	
Unknown	7 (1.5)	4 (<1)				
Slept near a fire as child				0.007		0.109
Yes	315 (66.9)	276 (58.6)	1.49 (1.12–1.97)		1.28 (0.94–1.75)	
No	155 (32.9)	195 (41.4)	1		1	
Unknown	1 (<1)	0				
Alcohol consumption				0.089		0.156
Current	144 (30.6)	129 (27.4)	1.08 (0.74–1.56)		0.91 (0.65–1.27)	
Former[f]	141 (29.9)	172 (36.5)	0.68 (0.46–1.01)		0.72 (0.51–1.01)	
Never	186 (39.5)	170 (36.1)	1		1	
Preferred beverage temperature				0.764		0.989
"Very hot" or "Hot"	414 (87.9)	410 (87.0)	1.08 (0.73–1.60)		0.99 (0.65–1.53)	
"Room temperature" or "Cold"	57 (12.1)	61 (13.0)	1		1	
Burnt mouth in past year				0.458		0.879
Yes	212 (45.0)	201 (42.7)	1.12 (0.86–1.45)		1.02 (0.76–1.37)	
No	258 (54.8)	270 (57.3)	1		1	
Unknown	1 (<1)	0				
Prior farmwork exposure				<0.001 [e]		0.001 [e]
Yes	376 (79.8)	297 (63.1)	2.46 (1.80–3.38)		1.75 (1.25–2.46)	
No	95 (20.2)	174 (36.9)	1		1	
Worked on a farm with pesticides				0.245		0.950
Yes	101 (21.4)	86 (18.3)	1.23 (0.89–1.71)		0.99 (0.69–1.42)	
No	370 (78.6)	385 (81.7)	1		1	
Direct contact with pesticides				0.294		0.613
Yes	85 (18.0)	72 (15.3)	1.22 (0.86–1.72)		0.91 (0.62–1.33)	
No	386 (82.0)	399 (84.7)	1		1	
Ate soil or clay as a child				0.007		0.016
Yes	79 (16.8)	50 (10.6)	1.73 (1.17–2.55)		1.67 (1.09–2.55)	
No	392 (83.2)	421 (89.4)	1		1	
Reused cooking oil				0.368		0.309
Yes	83 (17.6)	72 (15.3)	1.26 (0.81–1.96)		1.28 (0.80–2.05)	
No	321 (68.2)	341 (72.4)	1		1	
Unknown	67 (14.2)	58 (12.3)				
Preservation of grain/nuts				<0.001 [e]		0.002 [e]
Yes	378 (80.3)	303 (64.3)	2.27 (1.67–3.08)		1.65 (1.19–2.30)	
No	93 (19.7)	168 (35.7)	1		1	
Consume beans and magadi				0.501		0.309
Yes	114 (24.2)	123 (26.1)	0.88 (0.63–1.23)		0.83 (0.58–1.19)	
No	356 (75.6)	348 (73.9)	1		1	
Unknown	1 (<1)	0				
Gourd or calabash bowl use				0.538		0.208
Yes	49 (10.4)	56 (11.9)	0.86 (0.58–1.29)		0.75 (0.49–1.17)	
No	420 (89.2)	414 (87.9)	1		1	
Unknown	2 (<1)	1 (<1)				
Daily teeth cleaning				<0.001[e]		<0.001[e]
Yes	357 (75.8)	412 (87.5)	0.38 (0.26–0.56)		0.39 (0.26–0.60)	
No	113 (24.0)	55 (11.7)	1		1	
Unknown	1 (<1)	4 (<1)				
Well as water source				0.420		0.367
Yes	287 (60.9)	274 (58.2)	1.13 (0.86–1.47)		1.14 (0.85–1.53)	
No	184 (39.1)	197 (41.8)	1		1	
Running water in home				0.167		0.274
Yes	291 (61.8)	312 (66.2)	0.82 (0.62–1.07)		0.85 (0.63–1.14)	
No	180 (38.2)	159 (33.8)	1		1	

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Table 2. The associations of behavioral risk factors and lifestyle exposures with esophageal cancer. (Cont'd)

	471 Cases *N* (%)	471 Controls *N* (%)	OR[a] (95% CI)	*P*[b]	adj OR[c] (95% CI)	P_{adj}[d]
Household cooking site				0.158		0.127
Indoors, living space	14 (3.0)	9 (1.9)	0.75 (0.17–3.35)		0.99 (0.38–2.61)	
Indoors, separate space	229 (48.6)	254 (53.9)	0.81 (0.61–1.09)		0.73 (0.53–0.99)	
Outdoors	226 (48.0)	207 (43.9)	1		1	
Unknown	2 (<1)	1 (<1)				
Cooking site ventilated				0.010		0.029
Indoors, unventilated	16 (3.4)	9 (1.9)	1.75 (0.51–5.98)		0.58 (0.23–1.47)	
Indoors, ventilated	227 (48.2)	210 (44.6)	0.79 (0.58–1.06)		0.41 (0.16–1.03)	
Outdoors	226 (48.0)	251 (53.3)	1		1	
Unknown	2 (<1)	1 (<1)				
Firewood as cooking fuel				<0.001 [e]		<0.001 [e]
Yes	356 (75.6)	263 (55.8)	2.75 (2.01–3.77)		2.22 (1.59–3.10)	
No	115 (24.4)	208 (44.2)	1		1	

[a]Unadjusted OR and its 95% CI calculated on the basis of Cochran–Mantel–Haenszel test stratified by matched case–control pair.
[b]*P* value of unadjusted association test by Cochran–Mantel–Haenszel test. Comparisons do not reflect the unknown groups.
[c]Region-adjusted OR (adj OR) and its 95% CI based on conditional logistic regression model stratified by matched case–control pair.
[d]*P* value of region-adjusted association test (P_{adj}) by likelihood ratio test using the conditional logistic regression model. Comparisons do not reflect the unknown groups.
[e]Significance after Bonferroni correction ($P < 0.002$), which was corrected across all exposure measures.
[f]Former use was defined as last exposure >1 year prior.

Discussion

This case–control study provides a comprehensive assessment of sociodemographic, behavioral risk factors, lifestyle exposures, and food frequencies associated with ESCC in Tanzania, with a robust sample size. In our multivariable analysis, we identified significant associations of increased risk for ESCC with lower tertiles of IWI, status as a former smoker, second-hand smoke exposure in the home, permanent residence outside of the Eastern zone of Tanzania, daily consumption of spicy chilies, and daily consumption of salted foods. Daily consumption of raw greens, daily consumption of fruits, and daily consumption of smoked fish were identified as protective against ESCC in the multivariable analysis.

The role of tobacco exposure in the etiology of ESCC is well established. The increased risk of ESCC among smokers has been consistently demonstrated in various studies in the United States, Europe, Asia, and Africa (20, 26–31). In our study, 52% of cases identified as current or former smokers (19% current; 33% former), compared with only 39% of controls (13% current; 26% former). Self-reported former tobacco use was associated with increased risk of ESCC, and current tobacco also demonstrated a trend toward increased risk. This is consistent with studies from South Africa, Malawi, Kenya, Uganda, Zambia, and Zimbabwe which have found ESCC risk to be associated with tobacco smoking (7, 32–37). Nonetheless, the prevalence of tobacco use in Tanzania (14%) is lower than in other regions of the world, and the number of cigarettes smoked per day is likely lower among those who use tobacco, resulting in lower cumulative exposure to tobacco smoke (38, 39). Despite low overall rates of tobacco use in Tanzania and other parts of East Africa, national statistics may mask SES gradients in sub-Saharan African countries where the prevalence of tobacco use is highest in men and women with lowest SES (40, 41). In Tanzania, tobacco use rates are substantially higher in males (26% for males vs. 3% for females; ref. 42). It is notable that ESCC in the East African context is known to also disproportionately affect males to females in an approximately 2:1 ratio (8). A recent study from Uganda estimated the population attributable fraction of ESCC due to smoking as 20%, but concluded that it is unlikely that cigarette smoking alone explains the high incidence of ESCC in East Africa (20). In other settings, the population attributable fraction of ESCC attributable to tobacco and/or alcohol has been reported as significantly higher in men (43). Linkages of this disease to gendered behaviors in East Africa, including tobacco use, warrant additional investigation.

Our finding of the associations of both status as a former smoker as well as exposures to second-hand smoke in the household are consistent with recent estimates of 19% esophageal cancer disability adjusted life years (DALY) attributable to smoking in Eastern and sub-Saharan Africa (44). Polycyclic aromatic hydrocarbons (PAH) are carcinogens that exist in tobacco but also in the combustion products of other organic materials, including organic fuels such as coal and wood (45). In our analysis, several exposures possibly related to PAHs demonstrated trends toward increased risk, including use of an indoor unventilated cooking location, use of firewood as cooking fuel, and a history of sleeping near a fire as a child. These findings are consistent with the results of a recent meta-analysis which concluded that the use of solid biomass fuel for cooking or heating is associated with increased risk of ESCC (19). Thus, in addition to investigation of conventional tobacco use in this setting, context-specific PAH exposures warrant further exploration as putative contributors to increased risk for ESCC in East Africa and may be possible targets for development of prevention strategies.

Our results are notable for the absence of significant associations of ESCC with current or former alcohol consumption. Results from several smaller studies have historically reported mixed results regarding the role of alcohol in the etiology of ESCC in Africa (33–36, 38, 46). These analyses are confounded by small sample sizes as well as a wide range of alcoholic beverages consumed with varying ethanol content and ingredients. The recent ESCCAPE study, which was a case–control study contemporaneously conducted in western Kenya, recently reported that alcohol consumption, particularly consumption of local brews *buza* and *chang'aa*, is associated with greater than half of the ESCC burden in this population (16). While no significant association was detected with either current or former alcohol consumption in the Tanzanian population, self-reported "current alcohol use" may be

Table 3. The associations of self-reported food frequency with esophageal cancer.

	471 Cases *N* (%)	471 Controls *N* (%)	OR[a] (95% CI)	*P*[b]	adj OR[c] (95% CI)	P_{adj}[d]
Rice				<0.001[e]	0.74 (0.62–0.88)	0.001[e]
Daily	17 (3.6)	48 (10.2)	0.15 (0.03–0.68)		0.28 (0.14–0.56)	0.001[e]
3–5 times/week	115 (24.4)	114 (24.2)	0.74 (0.44–1.23)		0.67 (0.44–1.01)	
1–2 times/week	155 (32.9)	166 (35.2)	0.65 (0.44–0.95)		0.65 (0.46–0.94)	
<1 time per week	184 (39.1)	140 (29.7)	1		1	
Unknown	0	3 (<1)				
Wheat/bread/pasta				0.006	1.03 (0.88–1.20)	0.742
Daily	15 (3.2)	33 (7.0)	0.38 (0.14–1.08)		0.62 (0.31–1.25)	0.040
3–5 times/week	128 (27.2)	123 (26.1)	1.13 (0.76–1.69)		1.26 (0.88–1.81)	
1–2 times/week	123 (26.1)	91 (19.3)	1.53 (1.01–2.30)		1.47 (1.01–2.13)	
<1 time per week	205 (43.5)	223 (47.3)	1		1	
Unknown	0	1 (<1)				
Chipsi (fried potatoes)				0.105	0.91 (0.77–1.07)	0.246
Daily	21 (4.5)	31 (6.6)	0.62 (0.31–1.24)		0.63 (0.34–1.17)	0.190
3–5 times/week	45 (9.6)	39 (8.3)	1.05 (0.56–1.97)		1.15 (0.68–1.93)	
1–2 times/week	88 (18.7)	112 (23.8)	0.70 (0.49–1.00)		0.78 (0.55–1.11)	
<1 time per week	317 (67.3)	286 (60.7)	1		1	
Unknown	0	3 (<1)				
Beans				0.253	1.07 (0.91–1.27)	0.408
Daily	294 (62.4)	264 (56.1)	1.18 (0.62–2.25)		0.91 (0.50–1.67)	0.103
3–5 times/week	118 (25.1)	144 (30.6)	0.71 (0.23–2.25)		0.61 (0.32–1.16)	
1–2 times/week	28 (5.9)	29 (6.2)	0.33 (0.03–3.20)		0.71 (0.31–1.63)	
<1 time per week	31 (6.6)	30 (6.4)	1		1	
Unknown	0	4 (<1)				
Cooked greens				0.005	0.92 (0.79–1.07)	0.300
Daily	152 (32.3)	189 (40.1)	1.60 (0.73–3.53)		0.83 (0.50–1.37)	0.005
3–5 times/week	164 (34.8)	117 (24.8)	1.00 (0.51–1.96)		1.58 (0.97–2.59)	
1–2 times/week	100 (21.2)	98 (20.8)	1.25 (0.65–2.41)		1.17 (0.71–1.94)	
<1 time per week	55 (11.7)	65 (13.8)	1		1	
Unknown	0	2 (<1)				
Raw greens				<0.001[e]	0.68 (0.58–0.81)	<0.001[e]
Daily	25 (5.3)	59 (12.5)	0.22 (0.08–0.57)		0.26 (0.14–0.49)	<0.001[e]
3–5 times/week	68 (14.4)	81 (17.2)	0.47 (0.25–0.87)		0.56 (0.36–0.87)	
1–2 times/week	186 (39.5)	196 (41.6)	0.71 (0.50–0.99)		0.68 (0.49–0.94)	
<1 time per week	192 (40.8)	133 (28.2)	1		1	
Unknown	0	2 (<1)				
Pickled vegetables				0.301	0.97 (0.83–1.14)	0.722
Daily	25 (5.3)	39 (8.3)	1.00 (0.50–2.00)		0.65 (0.35–1.17)	0.215
3–5 times/week	50 (10.6)	49 (10.4)	0.88 (0.53–1.45)		1.20 (0.75–1.94)	
1–2 times/week	132 (28.0)	122 (25.9)	1.00 (0.71–1.40)		1.20 (0.85–1.69)	
<1 time per week	263 (55.8)	260 (55.2)	1		1	
Unknown	1 (<1)	1 (<1)				
Fruit				<0.001[e]	0.81 (0.69–0.95)	0.008
Daily	79 (16.8)	159 (33.8)	0.50 (0.21–1.17)		0.41 (0.24–0.70)	<0.001[e]
3–5 times/week	190 (40.3)	118 (25.1)	1.75 (0.95–3.23)		1.49 (0.94–2.37)	
1–2 times/week	124 (26.3)	115 (24.4)	0.88 (0.49–1.57)		1.05 (0.66–1.67)	
<1 time per week	77 (16.3)	76 (16.1)	1		1	
Unknown	1 (<1)	3 (<1)				
Smoked fish				<0.001[e]	0.86 (0.73–1.01)	0.073
Daily	22 (4.7)	64 (13.6)	0.08 (0.01–0.59)		0.31 (0.16–0.59)	<0.001[e]
3–5 times/week	175 (37.2)	150 (31.8)	1.44 (0.88–2.36)		1.18 (0.79–1.75)	
1–2 times/week	156 (33.1)	139 (29.5)	1.00 (0.63–1.59)		1.09 (0.73–1.61)	
<1 time per week	117 (24.8)	117 (24.8)	1		1	
Unknown	1 (<1)	1 (<1)				
Smoked meats				0.031	0.81 (0.68–0.97)	0.019
Daily	11 (2.3)	13 (2.8)	0.64 (0.25–1.64)		0.55 (0.22–1.37)	0.020
3–5 times/week	71 (15.1)	78 (16.6)	0.68 (0.42–1.10)		0.73 (0.48–1.12)	
1–2 times/week	142 (30.1)	175 (37.2)	0.67 (0.47–0.96)		0.60 (0.43–0.85)	
<1 time per week	247 (52.4)	204 (43.3)	1		1	
Unknown	0	1 (<1)				

(Continued on the following page)

Table 3. The associations of self-reported food frequency with esophageal cancer. (Cont'd)

	471 Cases *N* (%)	471 Controls *N* (%)	OR[a] (95% CI)	*P*[b]	adj OR[c] (95% CI)	P_{adj}[d]
Stewed or boiled meats				0.866	0.89 (0.75–1.06)	0.203
Daily	22 (4.7)	25 (5.3)	1.00 (0.38–2.66)		0.77 (0.38–1.54)	0.626
3–5 times/week	173 (36.7)	183 (38.9)	0.80 (0.44–1.44)		0.80 (0.51–1.25)	
1–2 times/week	181 (38.4)	175 (37.2)	0.97 (0.58–1.61)		0.93 (0.61–1.43)	
<1 time per week	92 (19.5)	83 (17.6)	1		1	
Unknown	3 (<1)	5 (1.1)				
Milk				0.223	0.86 (0.73–1.01)	0.072
Daily	14 (3.0)	25 (5.3)	NC[f]		0.36 (0.11–1.16)	0.056
3–5 times/week	72 (15.3)	84 (17.8)	0.67 (0.11–3.99)		0.59 (0.23–1.51)	
1–2 times/week	120 (25.5)	99 (21.0)	NC [f]		0.98 (0.39–2.47)	
<1 time per week	244 (51.8)	244 (51.8)	0.67 (0.24–1.87)		0.78 (0.32–1.90)	
Never	15 (3.2)	13 (2.8)	1		1	
Unknown	6 (1.3)	6 (1.3)				
Spicy chilies				0.001[e]	1.26 (1.10–1.43)	0.001 [e]
Daily	147 (31.2)	97 (20.6)	2.22 (1.36–3.63)		1.92 (1.29–2.88)	0.001 [e]
3–5 times/week	117 (24.8)	121 (25.7)	1.11 (0.66–1.87)		1.27 (0.85–1.92)	
1–2 times/week	55 (11.7)	74 (15.7)	0.79 (0.40–1.55)		0.84 (0.51–1.38)	
<1 time per week	152 (32.3)	179 (38.0)	1		1	
Maize meal				0.553	1.20 (0.95–1.51)	0.119
Daily	344 (73.0)	326 (69.2)	1.00 (0.35–2.85)		1.54 (0.54–4.38)	0.469
3–5 times/week	104 (22.1)	115 (24.4)	NC[f]		1.25 (0.42–3.68)	
1–2 times/week	14 (3.0)	19 (4.0)	NC [f]		1.02 (0.29–3.59)	
<1 time per week	9 (1.9)	10 (2.1)	1		1	
Unknown	0	1 (<1)				
Cassava				0.908	1.04 (0.90–1.19)	0.630
Daily	59 (12.5)	63 (13.4)	0.89 (0.45–1.74)		1.04 (0.63–1.71)	0.718
3–5 times/week	114 (24.2)	109 (23.1)	1.03 (0.66–1.58)		1.16 (0.80–1.69)	
1–2 times/week	102 (21.7)	96 (20.4)	1.15 (0.75–1.74)		1.22 (0.84–1.76)	
<1 time per week	196 (41.6)	200 (42.5)	1		1	
Unknown	0	3 (<1)				
Groundnuts/peanuts				0.599	1.07 (0.90–1.27)	0.468
Daily	17 (3.6)	16 (3.4)	1.43 (0.54–3.75)		1.15 (0.54–2.46)	0.851
3–5 times/week	61 (13.0)	48 (10.2)	1.89 (1.07–3.34)		1.21 (0.77–1.92)	
1–2 times/week	192 (40.8)	190 (40.3)	0.95 (0.70–1.30)		1.01 (0.74–1.38)	
<1 time per week	201 (42.7)	214 (45.4)	1		1	
Unknown	0	3 (<1)				
Salted foods				0.007	1.30 (1.05–1.62)	0.018
Daily	421 (89.4)	386 (82.0)	1.69 (0.85–3.36)		1.99 (0.99–4.00)	0.030
3–5 times/week	19 (4.0)	38 (8.1)	3.00 (0.31–28.84)		0.92 (0.38–2.22)	
1–2 times/week	12 (2.5)	14 (3.0)	2.00 (0.18–22.06)		1.37 (0.44–4.33)	
<1 time per week	19 (4.0)	31 (6.6)	1		1	
Unknown	0	2 (<1)				

[a]Unadjusted OR and its 95% CI calculated on the basis of Cochran–Mantel–Haenszel method stratified by matched case–control pair.
[b]*P* value of unadjusted association test by Cochran–Mantel–Haenszel test. Comparisons do not reflect the unknown groups.
[c]adj OR and its 95% CI based on conditional logistic regression model stratified by matched case–control pair.
[d]*P* value of region-adjusted association test (adj *P* value) by likelihood ratio test using the conditional logistic regression model. For each exposure, the first row is for the test of linear trend and the second row is for the test of nominal categorical levels of the food frequency responses. Comparisons do not reflect the unknown groups.
[e]Significance after Bonferroni correction ($P < 0.003$) across all food exposure measures.
[f]NC, not calculable due to insufficient sample size.

subject to confounding by indication amongst cases, as patients with ESCC may have discontinued drinking with onset of dysphagia and other cancer-related symptoms.

Similarly, we did not detect a link between reported hot beverage consumption and ESCC risk as has been reported in other settings in East Africa (13, 14). This is possibly explained by wide variation in self-reported and measured temperatures of hot beverages in the East African region (47), suggesting that additional research may be necessary to explore the role of hot beverages and best methodologic approaches to evaluate drink temperature.

Nitrosamines are an important carcinogen found in tobacco smoke and also presumed to be the main factor contributing to ESCC risk associated with poor oral hygiene and consumption of well water (48, 49), all of which are potentially associated with lower SES. Consistent with the existing literature (17, 49), ESCC cases in our population were less likely to report participation in daily teeth cleaning compared with matched controls. Although oral hygiene was not statistically significant in the final multivariable model, we did note the finding that a self-reported practice of daily oral hygiene trended toward a protective effect. In light of recent findings from

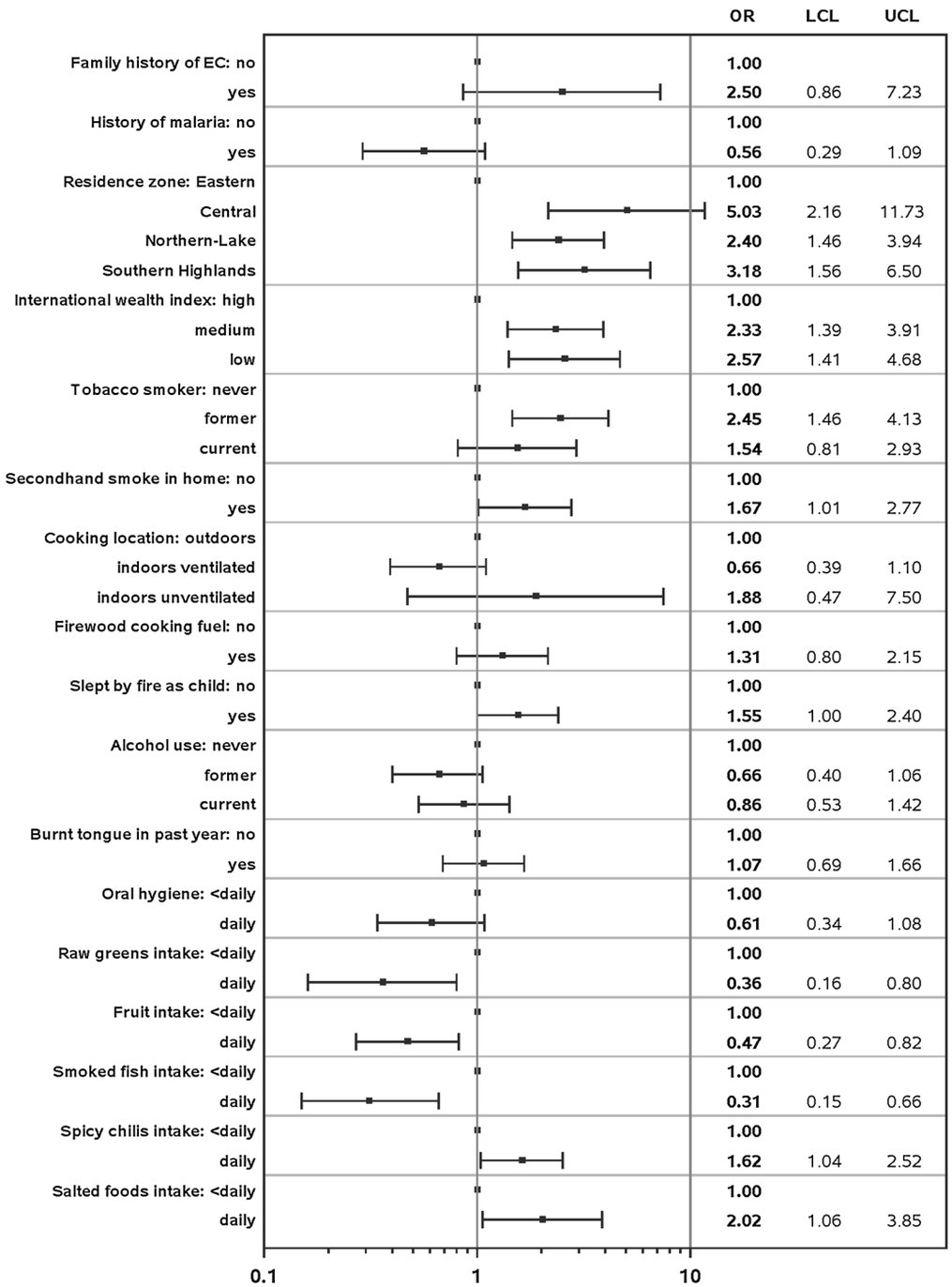

Figure 1.

ORs and 95% CIs for independent risk factors for esophageal squamous cell carcinoma in Tanzania as determined by a multivariate conditional logistic model ($N = 471$ cases and 471 controls). OR, odds ratio. LCL, lower 95% Wald confidence limit. UCL, upper 95% Wald confidence limit. Variables selected for inclusion in the model based upon both our novel findings in the univariate model *and* the existing literature on ESCC risk factors within Africa included: a family history of esophageal cancer, low SES (e.g., IWI score), PAH exposures (e.g., a history of tobacco smoke; a history of sleeping by a fire as a child, cooking location, firewood as cooking fuel; and second-hand smoke in home), dietary factors (e.g., low fruit and vegetable intake), and poor oral hygiene (12, 17). Additional variables selected for inclusion in the model based upon the results of our univariate model only included: a personal history of malaria, zone of permanent residence in Tanzania, intake of spicy chilies, intake of smoked fish, and intake of salted foods. Variables selected for inclusion based upon the existing literature but which did not emerge as significant in our univariate analysis included: a history of alcohol use, consumption of hot beverages (e.g., burnt tongue in past year).

Kenya reporting an association between poor oral health with increased risk of ESCC (17), the role of oral hygiene in ESCC warrants further evaluation. Moreover, the potential synergistic effects of poor oral hygiene with tobacco smoke and/or other PAH exposures in low SES populations warrant additional inquiry in the East African context.

Findings from previous studies which support the protective effects of daily consumption of fruits and raw greens (50, 51) were corroborated by this study. The role of fruits and vegetables in the reduction of risk for ESCC has been linked to the presence of several antioxidants as well as dietary components such as vitamin A, C, folate, and β-carotene. The finding of a protective effect of daily consumption of smoked fish was unexpected, however, and contradicts prior speculation that smoked fish may increase risk for ESCC as a prevalent exposure source for nitrosamines (52). Of note, fewer ESCC cases reported a permanent residence in the Eastern zone, where fishing is a dominant industry and food source and where the overall SES of the population is higher than in other regions of Tanzania. The significance of the protective effect of smoked fish was diminished in the region-adjusted analysis but remained statistically significant after Bonferroni correction across all food measures. In support of the multivariate model, higher consumption of both smoked fish and fruit were associated with higher IWI scores, whereas lower consumption of spicy chilies was associated with higher IWI scores. Associations were primarily driven by the highest frequency foods intake (e.g., daily). For both fresh fruit and smoked fish, the finding of a protective effect could be confounded by the higher SES associated with frequent access to these food groups. Neither consumption of salty foods and spicy chilies has been previously identified as risk factors in other settings, and both warrant further investigation into local methods of preparation.

Finally, the association of lowest IWI tertile was statistically significant in both our multivariable model and in the sensitivity analysis of cases with pathologic confirmation, pointing to some undetermined exposure or constellation of exposures that is associated with increased ESCC risk in populations with low SES in Tanzania. This is consistent with previous reports that low SES is a risk factor for ESCC, even after adjustments for tobacco, alcohol, age, and many other potential risk factors in Iran and globally (44, 48, 53). Certainly, there are myriad lifestyle factors that accompany low SES in East Africa, including increased risk of exposure(s) to smoke, use of biomass fuels for cooking and heating, pesticides and toxic chemicals, heavy metals from predominant use of unimproved surface water or well water, poor oral hygiene, and/or low intake of a healthy diet. In the Tanzanian population, a significantly higher proportion of ESCC cases reported an occupation in agriculture, which could be linked to an unidentified exposure. Notably, no significant association with pesticide exposure or farmwork exposure was detected in this analysis.

Potential limitations

Several limitations of this study must be acknowledged. First, recruitment of participants was from two national referral hospitals; thus, the participants may not be representative of ESCC cases and controls from throughout Tanzania. Although MNH and ORCI both are national referral hospitals and serve large catchment areas in Tanzania, cases were more likely than controls to reside outside the Eastern region (52% vs. 26%) where both institutions are located. To eliminate concerns regarding migration bias (54), we reviewed the complete residential histories provided and confirmed that nearly all participants (98%) were residents of the reported geographical zone within Tanzania for ≥20 years; less than 1% ($n = 7$) reported residence at the reported address for a duration <10 years. Thus, the higher proportion of ESCC cases from other regions of the country may reflect that cancer care is only available at few centers in Tanzania. ORCI was the only national cancer institute which offered radiotherapy during the study period; thus, a diagnosis of ESCC may be a condition for which patients are apt to travel longer distances for care, while patients with nonmalignant conditions receive care in smaller hospitals closer to home. In addition, the relatively higher SES of the Eastern zone of Tanzania where a majority of controls originated from might have introduced bias in the evaluation of variables related to SES. Cases and controls were matched for age and gender but were intentionally not matched for their region of permanent residence, based upon the premise that matching in the design of a case–control study does not control for confounding (55). To account for possible confounding caused by region, a region-adjusted conditional logistic model which included the corresponding variable plus region, provided strikingly similar results to the original model.

In addition, as in many case–control studies, hospital-based recruitment of cases inherently excludes cases who do not report to the hospital, resulting in potential for selection bias. For both cases and controls, we relied upon self-reporting. Stigma, associated with smoking and alcohol consumption in African cultural context, may have been subject to increased desirability bias due to selective underreporting. In addition, reporting of medical histories may be limited by low health literacy levels in Tanzania. We suspect that a family history of esophageal cancer may be underreported because of historic limitations around cancer diagnostics in Tanzania. We addressed the possibility of increased desirability bias through administration of the questionnaire in Swahili by two culturally matched members of the research team who performed interviews in private areas to maximize confidentiality and trust.

Finally, pathologic confirmation of ESCC was not required as part of the eligibility criteria for cases due to the numerous existing barriers to a pathologic diagnosis of cancer in Tanzania. As a result, our case population may have inadvertently included rare cases of esophageal adenocarcinoma or other diagnoses. However, based upon a more recent study we conducted in this same setting which utilized identical case ascertainment methods and did require pathologic confirmation (22), the fidelity of our ascertainment methods is presumed to be high. This was substantiated through the sensitivity analysis restricted to only case–control pairs with pathologically confirmed cases of ESCC, which yielded similar findings albeit with wider CIs due to reduced sample size. While we acknowledge the imperfection of inclusion criteria that allow cases on the basis of clinical findings only, this approach facilitated the efficient accrual of a robust sample size necessary for this study.

Conclusion

An estimated 17,992 incident cases of esophageal cancer were diagnosed in East Africa in 2018, almost all of whom will succumb to this diagnosis (56). There is profound urgency to identify high-risk populations within the region. Given the complexities and challenges of conducting large prospective cohort studies in this area, case–control studies are foundational to etiologic research in this setting. The present findings, along with those from the contemporaneous ESCCAPE case–control study conducted in Kenya (13, 16, 17), represent the earliest rigorous efforts to identify risk factors for the high burden of ESCC in East Africa and will inform the development of subsequent hypothesis-driven investigations. This article presents an initial comprehensive overview of a robust dataset from Tanzania. These results will inform future hypothesis-driven studies in effort to

identify environmental, molecular, and/or genetic susceptibility, as well as possible interactions. Research to evaluate to the high burden of ESCC remains a critical priority and will be necessary to inform development of prevention and early detection strategies that are relevant for the East African context.

Authors' Disclosures

L. Zhang reports personal fees from Dendreon, Smith-Kettlewell Eye Research Institute, and Raydiant Oximetry, Inc. outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

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Acknowledgments

Research reported in this publication was supported by the U.S. NCI of the NIH under award number P30 CA082103 (contract no. HH5N261200800001E). The content is solely the responsibility of the authors and does not necessarily represent the official views of the U.S. NCI or NIH. We thank the patients and their family members for their participation in this research study. We are grateful to each participating institution and to the ward nurses at Muhimbili National Hospital, Tanzania for assistance with case ascertainment. We acknowledge the members of the African Esophageal Cancer Consortium (AfrECC) for their ongoing scientific collaboration in East Africa. The authors acknowledge F. McCormick as principal investigator of the parent award (P30 CA082103) and K. Van Loon as the project leader.

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Received May 8, 2020; revised July 3, 2020; accepted October 22, 2020; published first November 3, 2020.

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