

Environmental risk factors for oesophageal cancer in Malawi: A case-control study

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Abstract

Aim

There is a high burden of oesophageal cancer in Malawi with dismal outcomes. It is not known whether environmental factors are associated with oesophageal cancer. Without knowing this critical information, prevention interventions are not possible. The purpose of this analysis was to explore environmental factors associated with oesophageal cancer in the Malawian context.

Methods

A hospital-based case-control study of the association between environmental risk factors and oesophageal cancer was conducted at Kamuzu Central Hospital in Lilongwe, Malawi and Queen Elizabeth Central Hospital in Blantyre, Malawi. Ninety-six persons with squamous cell carcinoma and 180 controls were enrolled and analyzed. These two groups were compared for a range of environmental risk factors, using logistic regression models. Unadjusted and adjusted odds ratios and 95% confidence intervals (CI) were calculated.

Results

Firewood cooking, cigarette smoking, and use of white maize flour all had strong associations with squamous cell carcinoma of the oesophagus, with adjusted odds ratios of 12.6 (95% CI: 4.2-37.7), 5.4 (95% CI: 2.0-15.2) and 6.6 (95% CI: 2.3-19.3), respectively.

Conclusions

Several modifiable risk factors were found to be strongly associated with squamous cell carcinoma. Research is needed to confirm these associations and then determine how to intervene on these modifiable risk factors in the Malawian context.

Introduction

Malawi, a resource-limited country in southeastern Africa, has a high burden of oesophageal cancer (OC).¹ OC is the second most common cancer in men and the third most common cancer in women, and age-standardized rates of OC are increasing.¹ In nearby African countries, OC incidence is estimated at 76/100,000, much higher than 2.2/100,000 in the United States.² In West Africa, OC is also rare.³

Oesophageal cancer is a devastating disease with a poor prognosis.⁴ In Malawi, the clinical scenario for OC patients is discouraging,⁵ owing to late presentation, minimal OC surgical expertise, no in-country radiotherapy, and availability of only basic chemotherapy. Prevention may therefore be the most effective tool for combating OC if modifiable risk factors can be identified. Understanding the modifiable causes of OC in Malawi is therefore an important public health priority.

Environmental exposures may be important risk factors for OC in Malawi. In other settings, cigarette smoking has been identified as an important modifiable risk factor for OC.⁶ In nearby African settings smoking pipe tobacco and

consuming local beer have been associated with OC.⁷ In Malawi, additional possible risk factors include consuming food contaminated with mycotoxins,⁸⁻⁹ the source of drinking water,¹⁰ the type and source of maize flour (*Zea mays*, or corn), the way maize is stored and processed, and the type of cooking method used. Specifically, wood-burning with subsequent release of polycyclic aromatic hydrocarbons (PAH) has been shown to be a risk factor in other settings.¹¹⁻¹³ On mycotoxins, our hypothesis was that *m'gaima* (whole grain maize flour), being the least processed type of local maize flour, harbours the most fumonisins and aflatoxins compared to other types of maize flour. Fumonisin and aflatoxins are types of mycotoxins produced by *Fusarium* and *Aspergillus* species of fungi, respectively, and have been associated with oesophageal cancer in other studies in the region,^{8,14-15} and in Iran.¹⁶ No epidemiological studies have been conducted in Malawi to explore potential environmental OC risk factors. One study in Malawi examined the geographic distribution of oesophageal cancer and found no geographic clustering, but this study did not examine specific environmental risk factors.¹⁷

We conducted a hospital-based case-control study to explore the association between multiple environmental risk factors and OC. This had not been done before in the Malawian context. Therefore, this was a hypothesis-generating study to explore modifiable environmental factors for OC in Malawi.

Materials and methods

Study design

This was a case-control study conducted at Kamuzu Central Hospital (KCH) and Queen Elizabeth Central Hospital (QECH), the two tertiary teaching hospitals in Malawi. This study was designed to compare a range of environmental exposures within the Malawi context. One hundred and thirty-three cases and 180 controls were enrolled from January 2011 to February 2013. Healthy controls were selected from both the KCH and QECH catchment areas. The study received ethical approval from the Malawi National Health Sciences Research Committee (NHSRC) and the University of North Carolina Internal Review Board (IRB).

Study population

Adult patients with suspected oesophageal cancer were identified in hospital wards and clinics by the study team, surgeons, and staff in the general surgery departments. Potential study participants were sent to cancer clinics or the endoscopy suites for eligibility evaluation and recruitment. Inclusion criteria for cases were: being 18 years of age or older; suspicion of OC based on clinical (odynophagia, dysphagia, weight loss and/or haematemesis), radiologic (barium swallow), or endoscopic (mass seen on flexible oesophageal endoscopy) means; and providing written informed consent. Potential cases had histological confirmation of OC after undergoing resection or biopsy, or had already received recent endoscopy with biopsy. Patients were excluded if the health care provider deemed it was unsafe to perform biopsy.

Unmatched healthy controls were recruited from among staff and visitors at KCH and QECH who were 18 years or older with no history of cancer. These persons came from the same catchment areas as cases, though not in a 1:1 ratio.

Individuals unable to give a clear past medical history were excluded as controls.

Clinical and laboratory procedures

Written informed consent was obtained, either in Chichewa or English, based on the participant's language competence. Trained personnel provided discussions of the consent in the participant's preferred language and answered participants' questions. If the participant was illiterate, the form was read to him or her in the presence of a witness. Participants consented with a thumbprint or signature, depending on literacy.

Thereafter, a study questionnaire was administered to obtain demographic details and known and possible risk factors for OC.

Histopathology analysis with haematoxylin and eosin staining of biopsy tissue was conducted on all cases. Oesophageal biopsy specimens were obtained by general surgeons specializing in endoscopy or by trained endoscopists using endoscopic biopsy forceps. The specimens were labelled, as per standard pathology protocol, with the patient name, hospital medical record number and, if known, date of birth; and accompanied by a laboratory request form. Specimens were transported in formalin and those obtained at KCH were processed at the KCH Pathology Laboratory. Specimens obtained at QECH were processed at the College of Medicine Pathology Laboratory in Blantyre. Haematoxylin and eosin slides were read by board-certified pathologists at KCH and the College of Medicine.

HIV status was determined through evaluation of health passports and hospital files. For those participants with unknown or undocumented status, rapid HIV testing was conducted. HIV test results were returned to participants on the same day.

Data management and analysis

Study information was entered into password-protected databases. Information for all cases was entered into a MySQL database run by Apache web server. Information for controls was stored in a study-specific password-protected Microsoft Access database. For data analysis, de-identified data sets from both cases and controls were converted into SPSS version 15.0 and concatenated into a single dataset. We restricted all analyses to squamous cell carcinoma (SCC), as the different types of OC may have different aetiologies and risk factors, and SCC was the only one we had sufficient power to explore. The analysis was further restricted to cases under 64 years of age ($N = 96$, 78%) because there were no controls 65 years or older, and thus no meaningful comparison population.

We explored several possible environmental risk factors: cigarette smoking, alcohol intake, cooking method, water source, and maize type and source. Cigarette smoking and alcohol use were dichotomized (never versus ever). Cooking method was categorized as charcoal, electricity, wood, or combination. Water sources were labelled as either treated (tap) water or untreated (e.g., river, borehole) water. There were several variables related to maize, the staple food in Malawi. We assessed type of maize, maize storage (sacks inside the house or in a granary), source of maize (self-grown or bought), and type of maize flour used (*m'gaima*, *gramil*, white, or combination). *M'gaima* is milled whole grain. *Gramil* is de-hulled, then milled. White maize flour is de-hulled, soaked, washed, dried and then milled. White maize

flour supposedly contains the fewest contaminants of the three types of maize flour.

Demographic variables included age, gender, and current occupation status. From participants' current occupation statuses, we derived their socioeconomic statuses, classified as "low-income", "medium-income", and "high-income". Low-income occupation groups included subsistence farmers and unemployed participants; medium-income occupation groups included manual workers (both skilled and unskilled) and domestic workers; and high-income occupation groups included professional, technical, managerial, clerical, sales, and services jobs.

Descriptive statistics included frequencies and percentages for categorical variables, and means and standard deviations for continuous variables. The distributions of these variables between cases and controls were compared using Chi-squared tests (categorical variables) and t-tests (continuous variables).

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals of each OC risk factor in unadjusted and adjusted analyses. Adjusted analyses were conducted to control for potential confounders. All models were adjusted for age, gender, and socioeconomic status. Some models were adjusted for other possible confounders, including cigarette smoke, wood burning, and source of maize.

Results

Eleven patients (7.6%) declined consent. Most of the OC cases ($n = 123$, 92%) were SCCs. Other histopathological types of OC included adenocarcinoma (2%), small cell carcinoma (2%), non-specific malignancy (2%), anaplastic carcinoma (1%) and non-Hodgkin's lymphoma (1%). There were 27 cases > 65 years of age who were also excluded. We therefore included 96 SCC cases and 180 controls for analysis (Table 1).

A higher proportion of cases (66%) than controls (39%) were male ($p < 0.001$) (Table 1). OC cases were older, with a mean age of 47.5 (SD 10.3) years, compared to 36.4 (SD 10.3) for controls. The majority of cases (70%) and half of the controls (50%) were selected from KCH. The majority (64%) of cases were in the lowest socioeconomic stratum, whereas the majority (70%) of controls were in the middle socioeconomic stratum ($p < 0.001$). HIV prevalence was similar in the two groups (20% in cases, 18% in controls, $p = 0.5$).

Among the oesophageal SCC cases, 40% had a cigarette smoking history, compared to 6% of controls. In unadjusted analysis, the odds of developing oesophageal SCC was 11.2 times higher among smokers than among non-smokers, and in adjusted analysis it was 5.4 times higher (Table 2). The adjusted model controlled for age, gender, socioeconomic status, and cooking methods.

Alcohol consumption was also more common in cases (36%) than among controls (20%). In unadjusted analysis, alcohol consumption was associated with developing oesophageal SCC (OR = 2.2). However, when controlling for age, gender, socioeconomic status, cooking methods, and cigarette smoking, it was no longer associated with oesophageal SCC (OR = 1.0), suggesting that the unadjusted relationship was driven by confounding factors.

The distribution of cooking methods differed considerably

Table 1: Characteristics of cases and controls

Category	Parameter	Cases (n = 96) [‡]	Controls (n = 180) [‡]	p-value
Age (yrs)	18-34	10 (10.4%)	87 (48.3%)	
	35-44	29 (30.2%)	59 (32.8%)	
	45-54	34 (35.4%)	22 (12.2%)	
	55-64	23 (24.0%)	12 (6.7%)	< 0.001
Sex	Male	63 (65.6%)	70 (38.9%)	
	Female	33 (34.4%)	110 (61.1%)	< 0.001
Study site	KCH	67 (69.8%)	90 (50.0%)	
	QECH	29 (30.2%)	90 (50.0%)	0.002
HIV status	Non-reactive	65 (79.3%)	145 (82.4%)	
	Reactive	17 (20.7%)	31 (17.6%)	0.5
Economic status	Low income	58 (64.4%)	29 (16.3%)	
	Medium income	24 (26.7%)	124 (69.7%)	
	High income	8 (8.9%)	25 (14.0%)	< 0.001

[‡]Category totals may not add up to column totals because of missing data.

KCH = Kamuzu Central Hospital, Lilongwe

QECH = Queen Elizabeth Central Hospital, Blantyre

Table 2: Environmental risk factors, food habits, and oesophageal cancer

	Cases (n = 96 [‡])	Controls (n = 180 [‡])	Unadjusted OR (95% CI)	Adjusted OR [†] (95% CI)
Cooking method:				
Charcoal	10 (10.6%)	65 (36.1%)	Reference	Reference
Combination	16 (17.0%)	70 (38.9%)	1.5 (0.6-3.5)	1.0 (0.4-2.7)
Electricity	2 (2.1%)	32 (17.8%)	0.4 (0.1-2.0)	0.4 (0.1-2.3)
Wood	66 (70.2%)	13 (7.2%)	33.0 (13.5-80.6)	12.6 (4.2-37.7)
Cigarette smoking:				
Never	56 (60.2%)	170 (94.4%)	Reference	Reference
Ever	37 (39.8%)	10 (5.6%)	11.2 (5.2-24.0)	5.4 (2.0-15.2)
Alcohol:				
Never	60 (64.5%)	144 (80.0%)	Reference	Reference
Ever	33 (35.5%)	36 (20.0%)	2.2 (1.3-3.9)	1.0 (0.3-2.9)
Maize storage:				
Sacks in the house	62 (68.1%)	121 (67.2%)	Reference	Reference
Granary	29 (31.9%)	59 (32.8%)	1.0 (0.6-1.6)	0.8 (0.3-2.2)
Source of maize:				
Buy	19 (20.7%)	124 (68.9%)	Reference	Reference
Grown own	73 (79.3%)	56 (31.1%)	8.5 (4.7-15.4)	3.1 (1.3-7.5)
Type of maize flour used:				
Gramil	17 (18.7%)	100 (55.6%)	Reference	Reference
Mgawwa	13 (14.3%)	35 (19.4%)	2.2 (1.0-10.1)	1.5 (0.4-5.5)
White	60 (65.9%)	40 (22.2%)	8.8 (4.6-17.0)	6.6 (2.3 - 19.3)
Combination	1 (1.1%)	5 (2.8%)	1.2 (0.1-10.7)	0.5 (0.0-7.3)
Water source:				
Treated (tap) water	27 (28.7%)	103 (57.2%)	Reference	Reference
Untreated (e.g., river or borehole) water	67 (71.3%)	77 (42.8%)	3.3 (1.9-5.7)	0.8 (0.3-1.9)

[‡]Category totals may not add up to column totals because of missing data.

[†]All odds ratios have been adjusted for age, gender, socioeconomic status, cooking methods, and smoking. The odds ratios for maize storage and type of maize flour have been further adjusted for source of maize.

among cases and controls. The majority (70%) of cases resided in households where firewood was used, compared to only 7.2% of the controls (Table 2). The majority of controls used either charcoal cooking (36%) or a mixture of cooking methods (39%). In unadjusted analysis, the odds of oesophageal cancer was 33.0 times higher among those who used firewood compared to those who used charcoal. In adjusted analysis, the odds of oesophageal cancer was 12.6 times higher among those who used firewood compared to those who used charcoal after controlling for age, gender, socioeconomic status, and cigarette smoking. This trend was stronger among women (OR = 85.3) than men (OR = 6.4).

Approximately two-thirds of cases and controls reported maize storage in the house as opposed to a granary. Most cases (79%) grew their own maize, compared to 31% of controls. Additionally, most cases (66%) used white maize, whereas most controls (56%) used *gramil*. Type of maize storage was not associated with oesophageal SCC in unadjusted (OR = 1.0) or adjusted (OR = 0.8) analysis. Growing one's own maize was moderately associated with increased odds of oesophageal cancer (adjusted OR = 3.1). Using white maize flour was strongly associated with oesophageal cancer (adjusted OR = 6.6) after controlling for age, gender, socioeconomic status, cooking methods, smoking, and source of maize.

Use of untreated water was more common among cases (71%) than among controls (43%). In unadjusted analysis,

water source was associated with developing oesophageal SCC (OR = 3.3). However, in adjusted analysis controlling for age, gender, socioeconomic status, cooking methods, and smoking, it was no longer associated with oesophageal SCC (OR = 0.8), suggesting that the unadjusted relationship was driven by confounding factors.

Discussion

Our findings suggest that wood cooking, cigarette smoking, and consumption of white maize flour were all associated with oesophageal SCC in our study population, while alcohol use, use of untreated water, and other environmental factors were not. These findings point to several modifiable factors that may contribute to the high incidence of SCC in Malawi.

The finding that wood cooking was strongly associated with oesophageal SCC offers a novel explanation for the high incidence of OC in Malawi. Wood burning is the predominant source of energy in Malawian homes, with 85% of households reporting the use of wood as fuel.¹⁸ In rural areas, the percentage of households using wood as fuel for cooking is considerably higher than in urban areas (94% versus 37%).¹⁸ Wood burning was found to be more strongly associated with OC than charcoal burning in our study. These are both considered dirty fuels.¹⁹ However, because wood burning uses a naked flame to heat items, whereas charcoal uses glowing embers, wood burning produces more particulate matter,²⁰⁻²¹ which contains products of incomplete combustion, such as PAH. A study in Sierra Leone found a higher prevalence of acute respiratory infections among children in homes with wood stoves, compared with homes with charcoal stoves.²² We could not compare the use of dirty fuels with the use of cleaner fuels, like electricity, because there were not enough electricity users in our study. But it is interesting to note that a study done in Mozambique, one of Malawi's neighbours, suggested that use of charcoal did not pose greater health risk than use of modern fuels (electricity and gas).²¹

Wood burning has been linked to oesophageal SCC in South Africa,²³ Iran,¹¹ and Brazil.²⁴ Use of wood-burning stoves typically occurs inside the home, where ventilation is poor, contributing to indoor air pollution. In Malawi, 68% of households cook indoors, especially in rural areas, where the majority of Malawians live.¹⁸ Malawian women tend to do most of the cooking, and we observed that firewood cooking was more strongly associated with SCC among women than men in a gender-stratified analysis. Indoor air pollution has also been associated with head and neck cancers, including OC, in high-risk areas of central and eastern Europe.²⁵ Head and neck cancers are prevalent in Malawi and are the fourth leading cause of cancer.

It has been postulated that high exposure to PAH may contribute to increased risk of OC.¹¹ Homes with wood-burning stoves tend to have higher levels of PAH than non-wood-burning homes.¹² Cooking by direct heat may also be another mechanism by which wood burning could contribute to oesophageal SCC. Broiling, barbecuing, and high-temperature cooking have shown association with oesophageal SCC.²⁶⁻²⁸ We did not study these aspects of cooking as risk factors, but we postulate that these could promote ingestion of PAH and thus could be contributory mechanisms for the association between wood cooking and oesophageal SCC.

Smoking is a well-described risk factor for oesophageal SCC, including in southern Africa.²⁹ To our knowledge, this is the

first time that smoking has been associated with SCC of the oesophagus in Malawi. However, 60% of the cases had never smoked, indicating that other risk factors must also play a significant role. Wood-burning stoves and cigarette smoking are both potential types of indoor air pollution. These types of indoor air pollution have also been linked to lung cancer and chronic obstructive pulmonary disease. These two diseases, together, were the third leading cause of death worldwide in 2011.³⁰ Strategies for addressing indoor air pollution would not only have potential impacts on the burden of oesophageal cancer, but also these other public health challenges. Intervention research to assess how to reduce exposure to indoor air pollution is therefore a public health imperative.

Maize is the staple food for Malawi; it is mainly consumed as flour and can be contaminated by mycotoxins at various stages of its production and storage. We found that growing one's own maize was moderately associated with oesophageal cancer, perhaps resulting from contamination during the growing process. In contrast, our finding that white maize flour has a stronger association with SCC of the oesophagus than *m'gaiwa* is counterintuitive. The production of white maize flour has less mycotoxin contamination than *gramil* or *m'gaiwa*.³¹ We expected *m'gaiwa* to have the strongest association with SCC. A possible explanation for the association of white maize flour with oesophageal SCC is lower fiber content in the white maize flour compared to the other less-refined forms of maize flour, such as *m'gaiwa*. The intake of fiber from whole grains has been associated with reduced risk for cancers of the aerodigestive tract.³² Another possibility is an unidentified toxin that is concentrated in white maize flour.

Control selection was imperfect. An important limitation of our study is that the majority of our controls were younger females of higher socioeconomic status than our cases, who were mainly poorer, older, male farmers. Additionally, because of the lack of older control subjects, we excluded the older oesophageal SCC patients. This was largely a result of the control selection process. Many of the controls were hospital staff or were recruited personally by hospital staff through convenience methods, because of time and resource constraints. We attempted to control for these factors through adjustment for age, gender, and socioeconomic status. However, our estimates may reflect bias from residual confounding.

Our study has several notable strengths. One strength is that all cases were histologically confirmed—a true challenge in our setting. Another important strength is that we had large numbers of cases and controls. Thirdly, we involved two hospitals whose combined catchment areas cover more than enough of Malawi's population to consider the study sample as representative for the country. Finally, it is desirable that controls reflect the population from which the cases are drawn, and our controls were a reasonable match for the population of Malawi, which is young with more women than men.

The risk factors for oesophageal SCC are likely multifactorial, including environmental exposures. Further research confirming these environmental risk factors, as well as the genetic-environment interactions, will be critical to the understanding of these relationships.

Our study suggests that wood-based cooking, smoking, growing one's own maize, and white maize flour are potential

risk factors for oesophageal cancer in Malawi. Research with better control of confounding to confirm associations and then, ultimately, to determine how to intervene on these modifiable risk factors (e.g., with alternative cooking methods), in the Malawian context, is needed.

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