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Risk Factors of Esophageal Squamous Cell Cancer in Southwestern Uganda: A Case-Control Study

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Abstract

Background: Despite the high rates and regional variations of squamous cell cancer of the esophagus (ESCC) in East Africa, little is known about the region specific risk factors. We aim to determine factors associated with ESCC in southwestern Uganda.

Methods: We conducted a case-control study of patients presenting for upper endoscopic examination from 2003 to 2014 at Mbarara Regional Referral Hospital, southwestern Uganda. Demographic and social data were collected prior to endoscopy including: age, gender, smoking status and alcohol use. Cases were those with a histological diagnosis of ESCC. Controls were participants with normal endoscopies or only gastritis. Patients with gastric cancer or peptic ulcer disease by histopathological examination or missing results were excluded. We used logistic regression to assess for association between age, sex, alcohol intake, and smoking with ESCC.

Results: Sixty-seven cases and 142 controls were included with a median age of 51 years (IQR 40 - 64); and male predominance (59.43%). Dysphagia and/or odynophagia were more frequent endoscopic indications in cases compared to controls (72.29% vs 5.56%, p<0.0001). Male gender (AOR 16.46, 95% CI 3.21 - 84.48, p=0.001), age group 41 to 50 years (AOR 13.32, 95%CI 1.16 - 15.3, p=0.038), and history of both alcohol and smoking (AOR 4.10, 95%CI 1.14 - 14.78, p=0.031) were associated with ESCC.

Conclusion: Our results emphasize the role of younger age, male gender, alcohol intake and smoking as risk factors for ESCC

in this population. Expediency and priority should be taken in early evaluation for esophageal cancer in southwestern Uganda in symptomatic patients with these risk factors.

Keywords: Esophageal squamous cell carcinoma; Substance use

Introduction

Despite a well described increase in adenocarcinoma, esophageal squamous cell carcinoma (ESCC) remains the predominant type of esophageal cancer worldwide[1]. In sub-Saharan Africa, incidence of esophageal cancer has regional variation with southern and eastern regions reporting significantly higher incidence rates[2]. Even within regions, there are within country variations[3]. These variations may be due to differences in risk factor profiles. In East African men, esophageal cancer is the second most commonly diagnosed cancer and the second highest cause of cancer deaths[4].

Most reports of esophageal cancer incidence from sub Saharan Africa are based on clinical diagnoses [3,5-7] because diagnostic upper gastrointestinal endoscopic examination and histology facilities are scarce in the region[7-9]. This inadvertently leads to inaccurate estimates since extraesophageal tumors may be misclassified as esophageal cancer and differentiation between adenocarcinoma and SCC is not possible[10-12]. Esophageal squamous cell carcinoma is fatal, with poor 5-year survival even in resource rich settings [13,14]. Therefore, risk factor modification and early detection for curable lesions offers a great opportunity to reduce ESCC mortality. Data from most countries describe risk factors for ESCC such as smoke and tobacco exposure, alcohol use [15], consumption of hot drinks [16], and diets low in fruit and vegetables [17], however there is limited data quantifying the exposure to these risk factors.

In Uganda, the incidence of ESCC is subject to considerable regional variation [18, 19] with three noticeable variations: the geographical distribution, the changing pattern of frequency with time, and gender disparity. Despite high rates and regional variation in squamous cell cancer of the esophagus in Uganda and East Africa [3], little is known about the region specific risk factors. We aim to determine risk factors associated with esophageal squamous cell carcinoma in southwestern Uganda.

Methods

Study Participants and Procedures

We carried out a case control study using data of all patients, aged 18 years or greater, who presented for upper gastrointestinal endoscopy from January 2003 to December 2014 at the Mbarara Regional Referral Hospital (MRRH), southwestern Uganda. It suffices to note that our endoscopy service was nonfunctional during 2010 to 2012. However, our center is the only endoscopy service in southwestern Uganda; receiving referrals from within MRRH and other health facilities; private and public in southwestern Uganda with an estimated population of 8.7 million people[20].

Before performing upper GI endoscopy, a standardized questionnaire collecting data including age, gender, history of alcohol and smoking, and symptoms, was administered after provision of informed consent for endoscopy & biopsy. An experienced endoscopist performed standardized diagnostic upper gastrointestinal endoscopy[21] using FN-30 fibre Olympus® gastroscopes, collecting tissue biopsies of both abnormal and normal mucosae. Per procedure, a minimum of three biopsies taken. Biopsies were kept in 10% buffered formalin before transportation to the histopathology laboratory at the department of Pathology, Mbarara University of Science and Technology for histopathology microscopic examination.

At the histopathology laboratory, all esophageal biopsies were processed into sections, stained with hematoxylin and eosin for 1 hour, and then examined using standard diagnostic criteria for microscopic atypia. Specifically, for esophageal squamous cell carcinoma, pathologist reported features such as presence of nuclear atypia, prominent keratinization and evidence of invasion[22].

The Mbarara University of Science & Technology research ethics committee approved this study.

Data Collection

We reviewed participants' records, first extracting cases of esophageal squamous cell carcinoma and then consecutively sampling the controls. For all participants, we collected pre-endoscopic data including age, gender, history of alcohol and smoking, and indication for endoscopy. We also reviewed diagnostic upper gastrointestinal endoscopy reports to collect information pertaining to the site of suspicious esophageal lesions i.e., upper third (15–24 cm), middle third (24–32 cm), and lower third (32–40 cm) esophageal lesions[23]. All data were doubly entered into an electronic database and cross-checked by two co-investigators to minimize entry and transcription errors.

Ascertainment of cases and controls

We defined a case as any participant having a histological diagnosis of esophageal squamous cell carcinoma either differentiated or undifferentiated. Controls were participants with normal endoscopic examination and normal histology or normal endoscopy except for the finding of gastritis. We excluded from the analysis participants with other histological diagnoses of other esophageal abnormalities such as esophagitis, esophageal adenocarcinoma, and Barrett's esophagus.

Statistical Analysis

We compared baseline characteristics between cases and controls using student t-tests and chi-square tests. We used logistic regression to identify correlates of histological diagnosis of esophageal squamous cell carcinoma. Our primary explanatory variables of interest were gender, age at presentation, history of smoking and alcohol, expressed as odds ratios with 95% confidence intervals. Associations between covariates and esophageal squamous cell carcinoma were estimated in unadjusted and multivariate models. All statistical tests were 2-sided. All analyses were performed with STATA version 13 (College Station, Texas, USA).

Results

Among 913 endoscopes performed at Mbarara Regional Referral Hospital between 2003 and 2014, there were 67 (7.3 %) new cases of esophageal squamous cell carcinoma. Among cases, males constituted 79.1% thus a male to female ratio of 4:1. (Table 1)

Table 1: Baseline characteristics of cases and controls

Characteristic	Control n=142, n (%)	Case n=67, n (%)
Male gender	75 (52.82)	53 (79.10)
Age group, years		
31- 40	29 (20.42)	2 (2.99)
41-50	28 (19.72)	19 (28.36)
51-60	32 (22.54)	16 (23.88)
61-70	27 (19.01)	16 (23.88)
> 70	22 (15.49)	11 (16.42)
Missing	4 (2.82)	3 (4.48)
Substance abuse		
Smoking	8 (5.63)	6 (8.96)
Alcohol	22 (15.49)	6 (8.96)
Alcohol & smoking	10 (7.04)	14 (20.90)
Presenting symptoms		
Dyspepsia	77 (54.23)	_
Dysphagia	14 (9.86)	38 (56.72)
Dysphagia & weightloss	4 (2.82)	6 (8.96)
Regurgitation[Υ]	8 (5.63)	1 (1.49)
Odynophagia	4 (2.82)	8 (11.94)
Upper GI bleeding[Ψ]	16 (11.27)	_
Others[α]	18 (12.68)	6 (8.96)
Dysphagia & Odynophagia	1 (0.70)	8 (11.94)
HIV positive	2 (1.41)	2 (2.99)

Upper GI bleeding[Ψ]:hematemesis and/or melena; Regurgitation[Υ]: Epigastric pain, heartburn and/or regurgitation Others[α]:vomiting, abdominal pain, and chest pain

Among the 142 controls; 30 (21.1%) had normal histology and 45 (31.7%) had gastritis/duodentitis. There was slightly higher proportion of males among cases compared to controls (79.1% vs 52.82%). The age distribution was similar among cases and controls except for < 41 years with a higher proportion of controls. (Table 1)

As expected, indication for endoscopy were significantly different between cases and controls, for example, dysphagia and/or odynophagia were significantly more frequent endoscopic indications in cases compared to controls (72.29% vs 5.56%, p<0.0001). (Table 2) Overall, the common sites for esophageal masses were the lower and mid portions of the esophagus in 28 (41.79%) and 21 (31.34%) respectively. Self reported HIV infection rates were similar between these groups. Of note, 42 (93%) patients with gastritis had positive CLO test results.

Table 2: Endoscopic examination features of cases and controls

Endoscopic features	Control n=142, n (%)	Case n=67, n (%)
Normal	30 (21.13)	_
Upper esophageal mass	_	5 (7.46)
Mid esophageal mass	1 (0.70)	6 (8.96)
Lower esophageal mass	8 (5.63)	21 (31.34)
Esophageal mass (unspecified location)	2 (1.41)	28 (41.79)
GE junctional mass	4 (2.82)	2 (2.99)
Gastritis	45 (31.69)	1(0.49)
Others[λ]	83 (58.45)	2 (2.99)
Missing	14 (9.86)	2 (2.99)
Rapid urease (CLO) positivity	42 (29.58)	9 (13.43)

Others[λ]: gastritis of unspecified location; CLO: Campylobacter like organism

Table 3: Univariate and multivariate logistic regression models evaluating risk factors for squamous cell carcinoma of the esophagus.

Characteristic	Univariate Model OR (95 % CI)	p-value	Multivariate Model Adjusted OR (95 % CI)	p-value
Female gender	REF		REF	
Male gender	3.33 (1.69 – 6.55)	0.0001	16.46 (3.21 - 84.48)	0.001
Age category				
31 – 40	REF		REF	
41- 50	9.84 (2.09 – 46.21)	0.004	13.32 (1.16 - 15.3)	0.038
51 – 60	7.25 (1.53 - 34.28)	0.012	5.71 (0.54 - 60.31)	0.147
61 – 70	8.59 (1.80 – 40.92)	0.007	6.94 (0.63 - 76.75)	0.114
> 70	7.25 (1.46 - 36.10)	0.016	5.68 (0.55 - 58.92)	0.145
Substance use[µ]				
Smoking	5.25 (1.39 - 19.69)	0.014	2.47 (0.53 - 11.40)	0.247
Alcohol	1.91 (0.57 - 6.34)	0.291	1.98 (0.48 - 8.19)	0.347
Alcohol & smoking	9.8 (3.15 - 30.45)	0.0001	4.10 (1.14 - 14.78)	0.031
Rapid urease test positivity	0.32 (0.07 - 1.38)	0.126	_	_
HIV infection	3.68 (0.49 - 27.64)	0.205	_	_

Substance use[µ]: self reported current or former use

In the univariate logistic regression modeling, Age (each 10 year increase), male gender, both alcohol & smoking were significantly associated with a diagnosis of ESCC. On multiple logistic regression (Table 3), we found male gender (AOR 16.46 (3.21 - 84.48), p=0.001), age group of 41 to 50 years (AOR 13.32 (1.16 - 15.3), p=0.038), history of both alcohol intake

and smoking (AOR 4.10, 95%CI (1.14 - 14.78), p=0.031) were independently correlated with esophageal squamous cell carcinoma.

Discussion

The present study identifies several important factors associated with an endoscopic & histological diagnosis of ESCC. Our study is the first, to our knowledge, to describe a younger age (41-50 years) as important risk factor for esophageal squamous cell carcinoma in Uganda. Of note, our participants with esophageal cancer generally presented at a younger age (median 44 years (IQR 32 - 54)) compared to counterparts in central Uganda who present at median 66 years[19]. Globally, esophageal squamous cell cancer is a disease that occurs in the late 6th and 7th decades of life [24] and cases occurring before the age of 40 years are rare[25]. However, our finding is similar to reports from southwestern Kenya, which showed a significant number of esophageal cancer patients presenting at younger ages [25, 26]. Taken together, we posit that maybe there is a peculiar genetic predisposition and or environmental carcinogenic risk factor for ESCC that may be present at an early age and or is rapidly progressive to explain the younger age of ESCC presentation in this region. Further evaluation is needed to determine these risk factors.

Our findings of male gender, and substance abuse (smoking and alcohol use) as factors strongly associated with ESCC are similar to reports from the northern [18] and central Uganda [19], and East Africa [25, 27] and other regions with high incidence of ESCC [28, 29]. Superimposed is the background of poverty and poor nutritional status that is rampant in this setting and has been shown to be risk among African Americans[30]. Further study to specify smoking duration, and methods e.g., as a cigarette, in pipes, as pipe tobacco rolled in paper or as domestic smoke, to quantify smoking risk for esophageal cancer development and to quantify alcohol use and duration are needed[31]. Despite a polymorphic predisposition to esophageal squamous cancer in light to heavy drinkers triggered by severe acetaldehydemia [32], there has been conflicting evidence for role of alcohol as a risk factor for ESCC with some studies showing moderate or higher risk within the high-risk population[15, 33]. Prospective study of ESCC with precise alcohol consumption quantitation is required to improve estimates of risk in this setting.

This data should be interpreted in the context of the study design. Mostly, the patients studied were at a referral center and thus maybe an inaccurate representation of the general population compared to patients in community outreach centers. Also, smoking and alcohol status was based on previous or current use, and precise quantitation was not possible. As with all non-randomized observational studies, our study could suffer from unmeasured or residual confounding on the associations between younger age (< 40years) and ESCC. However, given that our results are similar to findings in high-risk populations, such confounders are more likely to represent actual mediators of the relationship between young age male and ESCC, than true confounder per se.

In conclusion, our results emphasize the role of male gender, alcohol intake and smoking as risk factors for ESCC in this population moreover at a younger age than reported in high risk populations in resource rich settings. Expediency and priority should be taken in early screening for esophageal cancer in southwestern Uganda. Future work should focus on relationships between modifiable risk factors i.e., smoking and alcohol use; as well as evaluate preventative and interventional strategies to reducing ESCC risk in this population.

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