Risk Factors for Esophageal Squamous Cell Carcinoma in a Kenyan Population

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Abstract

Background: Esophageal squamous cell carcinoma (ESCC) is common in some parts of Kenya. Both the regional factors associated with ESCC in Kenya and geographic distribution has not been completely described. **Methods**: We analyzed the association of ESCC with smoking, khat chewing, alcohol, diet, socioeconomic status, caustic ingestion and first degree family history of ESCC in a multi-center based matched case-control study. We also determined the geographic origin, age, gender and ethnicity of patients visiting the participating centers between August 2008 and April 2009. **Results**: Eighty three cases and 166 controls matched for age and gender were studied. The male to female ratio of cases was 2.1:1, majority were from Central and Eastern provinces of Kenya, about one fifth (19%) were younger than 45 years of age. On multivariate analysis, caustic ingestion (OR 11.3 CI 3.0 – 42.5), first degree family history of ESCC (OR 3.5 CI 1.3 – 9.5) and poor housing (OR 2.0 CI 1.1 – 3.5) were independent predictors. **Conclusions**: Majority hailed from the Central and Eastern provinces probably due to proximity to the study centres. A large proportion of cases were young compared to studies in other high incidence regions in the world. Low socio-economic status, family history of ESCC and a history of caustic ingestion were significant risk factors.

Key Words: Esophageal, Squamous Cell Carcinoma, Risk Factors, Kenya

Introduction

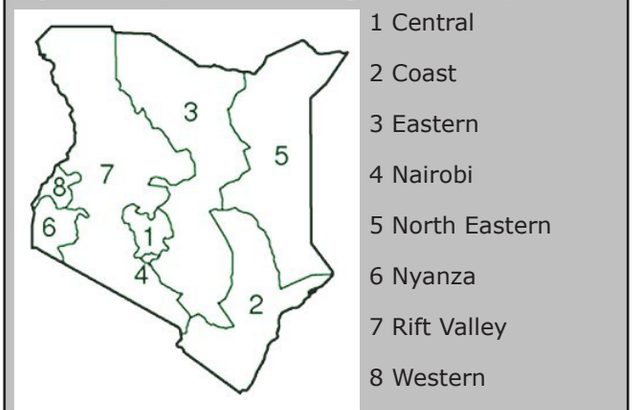
Esophageal squamous cell cancer (ESCC) is common with a global incidence of 5.2 per 100,000 (7.7 in men and 2.8 in women). The highest estimated national rates are those of China, Malawi, Turkmenistan, Kenya, Mongolia, Uganda and South Africa (1,2). The onset of esophageal squamous cell carcinoma (ESCC) is insidious with the disease becoming clinically overt in advanced stages. In Kenya, ESCC is the second most common malignancy in adult males and the ninth most common cancer overall with an incidence of 9.1/100,000 (3). Delayed presentation and lack of access to health care results in high morbidity and mortality (4.5). Prevention is hampered by limited information on the etiology and region-specific risk factors in Kenya. Therefore, determination of the demographics and description of specific regional risk factors within Kenya is worthwhile. The proposed risk factors in this study are based on findings from areas of high incidence such as China, South Africa, Tanzania and Ghana. These factors include alcohol, smoking, hot tea and exposure to potential carcinogens in diet (6-9). At the time of conducting this study, no other investigation had been conducted within Kenya to establish any association and the extent thereof with any risk factors. Subsequently, other studies in Kenya have identified areas of high incidence in Western and Rift Valley provinces (10-11). Khat chewing is common in Central, Eastern and North Eastern provinces of Kenya particularly among the males. In-vitro and animal model experiments have shown both direct and indirect effects of Khat on the esophageal mucosa (12, 13).

The aim of this study was to test for any association between development of ESCC and exposure to the risk factors including khat chewing among patients visiting the participating centers.

Methods

Between August 2008 and April 2009, we conducted a multi-center, age and gender 1:2 matched case - control study. The participating centers were selected on the basis of case volume, geographical location and institutional approval (Figure 1). Cases were defined as adult Kenyan residents 18 years of age and above with ESCC confirmed on histology. Controls were selected randomly from the individuals visiting the same center at the same time period. Exclusion criteria for controls were dysphagia, history of malignancy and cognitive or memory impairment. Consecutive incident cases were selected according to the inclusion and exclusion criteria after confirmed ESCC on histopathology of endoscopic biopsy specimens. For each case two controls were selected randomly from individuals visiting the same center and matched for age (±5 years), gender and geographic origin prior to interview. Demographic information and degree of exposure to the proposed risk factors was obtained by means of a questionnaire. Details on the diet, tea and smoked foods were collected by means of a food frequency chart. Information on the hypothesis being tested in the study was not disclosed to the study subjects prior to the interview. Application of the questionnaire was by trained medical personnel. Training of the interviewers was done by the principle investigator and co-investigators. It involved role playing and test runs prior to commencement of the study.

Figure 1: Kenya administrative provinces (study sites)



The data collected included patient age, gender, province of origin, ethnic group, information on exposure to various risk factors, dietary intake and confounding factors (history of diabetes and coronary artery disease). The data was checked and verified by the co-investigator and principal investigator before entry into the database.

Sample size was calculation was based on the aim to detect a two fold increase in ESCC among patients exposed to the variable with least expected impact (khat chewing), a p-value of less than 0.05 at a power of 80%.Controls were matched to cases at a ratio of 2:1, with the appropriate adjustment factor of 0.75 according to Kirkwood and Sterne (31). The required sample size was 120 cases.

The distribution of the risk factors between cases and controls was compared using chi-square tests. Significance was defined as a 2-tailed p-value less than 0.05. Data was analyzed in SAS System for Windows version 8.0. Significant factors on univariate analysis were further subjected to multivariate analysis to determine independent factors.

Results

We had a total of 91 cases and 182 controls from which we excluded 8 cases and 16 controls due to lack of histological confirmation of ESCC for the cases. Eighty three cases and 166 controls were used in the final analysis.

The cases and controls were comparable in co-morbidity profile (Table 1) and the majority of the subjects were recruited from St. Mary's Mission hospital in Nairobi (Figure 2). Forty two percent of the cases were 54 years of age or younger (Table 2). Most cases and controls were from Eastern and Central provinces (Table 3).

Twelve of 80 cases had a history of caustic injury compared to only 3 of 161 controls, 10 out of 83 cases had a first degree relative with ESCC compared to 8 of 164 controls. The cases were also of a lower social-economic status based on the type of housing, education and type of cooking fuel used (Table 4).

On univariate analysis the risk of developing ESCC was higher for caustic ingestion, poor housing, family history of ESCC, a low education level, and cigarette smoking. Chewing khat, ingestion of alcohol, tea and a staple diet consisting of starch were not associated with development of ESCC (Table 5).

The following three risk factors, on multivariate analysis, were significantly associated with ESCC: Caustic ingestion (OR 11.35 CI 3.04 – 42.46), First degree family history of ESCC (OR 3.50 CI 1.29 – 9.49) and poor housing (OR 1.98 CI 1.11 – 3.53) (Table 6).

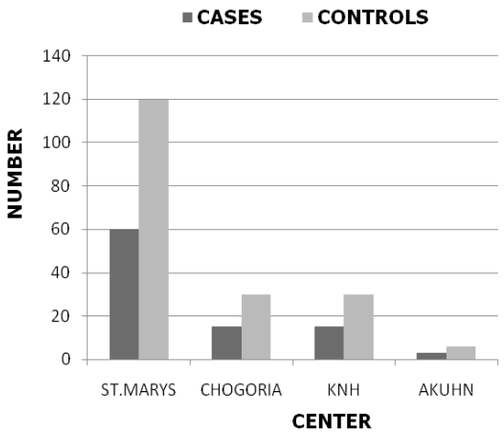
Table 1: case: control comparison for age, gender and co-morbidity. * History of coronary artery disease

	Cases	%	Controls	%	P-value
AGE					0.4639
(Years)	56.9±13.8		55±12.9		
Mean ± SD	58		55		
Median	29-81		28-81		
Range N	83		164		
Females	26	31.3	52	30.5	
Males	57	68.7	114	69.5	0.8931
Diabetics	12	14.5	21	12.9	
Non diabetics	71	85.5	142	87.1	0.7324
CAD*	0	0.0	2	1.2	
No CAD*	83	100.0	162	98.8	0.5520

Table 2: Age and Gender distribution among cases and controls.

	Age: mean (range)	
	Cases	**Controls**
Male (range)	58.5 years (29-81)	56.1 years (28-81)
Female (range)	53.3 years (29-79)	52.6 years (28-77)

Figure 2: Distribution of cases and controls according to study centre



(KNH – Kenyatta National Hospital, AKUHN – The Aga Khan University Hospital Nairobi)

Table 3: Distribution of cases and controls according to province of origin

PROVINCE	Cases n (%)	Control n (%)
NAIROBI	5 (6)	31 (18.6)
CENTRAL	15 (18)	30 (18)
WESTERN	7 (8)	17 (10.2)
COAST	3 (4)	5 (3)
RIFT VALLEY	5 (6)	14 (8.4)
EASTERN	31 (37)	51 (30.7)
NORTH EASTERN	7 (8)	5 (3)
NYANZA	5 (6)	9 (5)
TOTAL	**78**	**152**

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Table 4: Rates of exposure to smoking, alcohol and khat chewing between cases and controls

	CASES (%)	CONTROLS (%)	OR (C/I)
Caustic injury	12 (15.0)	3 (1.9)	9.3 (2.5-34.0)
No caustic injury	68 (85.0)	158 (98.1)	
Pos. Fam Hx	10 (12.o)	8 (4.0)	2.7 (1.0-7.0)
Neg. Fam Hx	73 (88.0)	156 (94.1)	
Wooden / Mud house	49 (59.0)	75 (45.7)	1.7 (1.0-2.9)
Stone house	34 (41.0)	89 (54.3)	
Firewood/Charcoal	67 (80.7)	119 (72.6)	
Gas/Electricity	16 (19.3)	45 (27.4)	
None/Primary school	51 (61.4)	79 (48.1)	1.7 (1.0-2.9)
Secondary/ University	32 (38.6)	85 (51.9)	
Alcohol history	38(49)	63(41)	1.0 (1.0-1.0)
No alcohol history	39 (51)	89 (59)	
Khat chewing	10(12)	20(12)	1.0 (0.98-1.02)
No khat chewing	73 (88)	143 (88)	
Cigarette smoking	37 (57.8)	27 (42.2)	1.05 (1.02-1.09)
No smoking history,	41 (23.3)	135 (76.7)	

Table 6: Multivariate analysis of factors of interest

FACTOR	O R	95%C I
CAUSTIC INGESTION	11.35	3.04 - 42.46
FAMILY H/O ESCC	3.50	1.29 - 9.49
HOUSING	1.98	1.11 - 3.53

Discussion

ESCC is a common malignancy in Kenya and is characterized by a high incidence among young patients (1, 3). In our study, a fifth of the patients were younger than 45 years. Wakhisi and colleagues found a median age of 58.7 at diagnosis with the youngest patient being 20 years old (5).White et al noted a high incidence of ESCC among young patients with 11% presenting at 30 years of age or less (10). Dawsey and colleagues described a case series of 109 patients with ESCC at the age of 30 years or less presenting to a single center (14). From the region, similar age characteristics have been described in Malawi and Mozambique (15). This contrasts with results from several high incidence areas in the world, where the patients are much older and rarely less than 30 years (6,16-17). It is unclear whether this young age represents a true difference or is a reflection of lower life expectancy in Kenya. Although we have not adjusted the incidence rates to age, the early presentation recorded in the Kenya patients may point to possible hereditary genetic aberrations and early transmissible agents that may cause genetic and epigenetic changes leading to ESCC. The nature of these agents is so far a matter of conjecture. One agent that has been tested with mixed results is HPV infection (18).

In our study, the cases were mostly from Eastern and Central provinces probably due to the proximity of these regions to our study centres. More than three decades ago Ahmed and Cook had shown that Western Kenya was a high incidence region (19,20). Later, Gatei and colleagues showed that Central province was also involved (21). More recently, Wakhisi et al. and White et al have identified Bomet district and parts of Western Kenya to be high incidence areas (5,10). These areas provide unique environmental and cultural features that could inform future studies to link the disease distribution and prevailing risk factors.

The male to female ratio was 2.2:1 among the cases. This differs slightly from the findings reported by White et al and Wakhisi et al with ratios of 1.4:1 and 1.5:1 respectively (5,10). It is likely that we had a mixed population of patients from both high and low incidence areas. The ratio is 1:1 in the high incidence areas of China and Iran and 6:1 in the low incidence areas within the same country (6, 17). The slightly higher male preponderance in our study compared to other studies within Kenya is likely due to the limited geography and small sample size besides the possible mixture of high and low incidence regions.

Caustic ingestion was associated with ESCC (OR 9.29, C/I 2.51-33.98). The wide confidence interval indicates a small sample size. Earlier follow-up studies have shown an association between esophageal corrosive injury and development of ESCC at up to 71 years with most cases being diagnosed more than 30 years from the time of injury. The ingestion leads to a stricture in the esophagus and increases the risk of developing ESCC by 1000 to 10,000 (22, 23).

This study has shown that poor housing increased the odds of developing ESCC by 1.7. Characterized by semi-permanent wooden to mud structures with poor ventilation, this mode of housing is a marker of low socio-economic status which has been shown to be associated with ESCC in both the developed and developing world (24, 25).The current results indicate that individuals with a first degree relative with ESCC were at a higher risk for developing ESCC. While genetically transmissible factors for ESCC have not been reported, it is possible that this finding is due to similar social and environmental factors among members of the same family. The question of which came first, whether genetic predisposition and an environmental or social/cultural factor(s), remains largely unanswered since no germ line genetic mutation with high penetrance has been associated with ESCC. It is, however, still a worthwhile endeavor to identify familial clustering of the disease and look for any genetic and epigenetic changes that may lead to the disease or render an individual more susceptible to development of the disease once he/she is exposed to certain external factors. An underlying predisposition may be explained by differences in metabolism in injurious agents like alcohol (26, 27).

We did not find any association between khat chewing and ESCC. Khat extract has been shown to cause genetic mutations and induce chromosomal aberrations in bacteria and also cause micronuclei formation in bone marrow cells of mice (28, 29). Studies in Yemen and Saudi Arabia showed a correlation between khat chewing and the development of head and neck cancers (30). The effect of khat appears to be maximal at the site of storage of the chewed bolus over the buccal mucosa due to the increased contact time. Within the esophagus, Khat may not play a significant role since it is neither corrosive nor does it have a long contact time. Furthermore, a good number of khat chewers also smoke, drink alcohol and may be of a

low socioeconomic class and, therefore, it becomes difficult to ascribe development of ESCC to the habit alone. The khat-ESCC theory may be difficult to confirm. It will require a much larger study population, over a longer time frame, to control for smoking, alcohol and socio-economic status.

We did not find any association with a diet rich in starch or any protective effect from vegetables and fruit. The staple diet of all those interviewed was composed mainly of starch based meals and, therefore, it might be difficult to show a difference in their effects.

This study has limitations. Being a case-control study the main limitation of the study is the inability to verify the information given by the study subjects. It was difficult to exclude asymptomatic controls unless they were all subjected to endoscopy. However, even endoscopy would have a false negative rate for early disease depending on the number of biopsies and the pathological examination. A population of controls from the endoscopy suite would be biased in terms of economic and social status since not all patients who require the procedure are able to afford and access it.

An attempt at reducing selection bias by including patients from a private hospital and the subsidized centers was not successful due to the small number of cases in the former. It also has an inherent recall bias since cases would be motivated to remember any event that may explain the disease process.

Conclusions

Most of the patients studied were from Central and Eastern province of Kenya probably due to the proximity of the centers to Nairobi. In this population, ESCC seems to present at a relatively younger age when compared to other high incidence regions in the world. This study also found a higher male preponderance probably due to an admixture of both high and low incidence populations. Poor housing, family history and caustic ingestion were each associated with increased odds of developing ESCC in the population studied.

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