Original Article

HIV AND ESOPHAGEAL CANCER IN MOZAMBIQUE: WHAT CAN WE LEARN?

VIH E CANCRO DO ESÓFAGO EM MOÇAMBIQUE: O QUE É QUE APRENDEMOS?

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ABSTRACT

Esophageal cancer (EC) is common cancer in Mozambique, with esophageal squamous cell carcinomas (ESCC) being the most frequent subtype of this cancer. Little is known about the impact of the human immunodeficiency virus (HIV) on this pathology. The main goal of this study was to assess the association between EC and HIV infection. **Methods:** A case-control study was conducted, in 2018, at Maputo Central Hospital, Mozambique (MCH). Consenting adults were eligible for inclusion. Patients with ESCC who underwent HIV testing constituted the case groups. Controls were selected from patients with surgical benign conditions, and they were matched by sex and age. Chi-square or Fisher's exact tests were used to evaluate the association between two categorical variables. Comparisons between groups were performed, using independent samples t-tests or Mann–Whitney tests for continuous variables. Odds Ratio (OR), and the corresponding 95% confidence interval (CI) were computed using non-conditional logistic regression. A p-value < 0.05 was considered significant. **Results:** During the study period, 92 cases and 92 controls were enrolled into the study. 67.4% of the cases were female. The median age of cases and controls was 57 (35-83) and 52 (35-85) years, respectively. HIV-positive diagnosis significantly increased the odds of developing EC, mainly in females (OR=4.81;

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95% CI: 2.24–10.32; p<0.001), but the same did not occur in males (OR=2.26; 95% CI: 0.80–6.36; p=0.123). **Conclusion:** Esophageal cancer and human immunodeficiency virus are common in Mozambique. HIV infection is a potential risk factor for ESCC mainly in the female gender. Patients with HIV and other risk factors such as exposure to domestic or tobacco smoke should be educated and followed up for an early diagnosis of esophageal cancer.

Keywords: *esophageal cancer, HIV, Mozambique.*

RESUMO

O cancro do esófago (CE) é um cancro comum em Moçambique, sendo os carcinomas de células escamosas do esófago (CCEE) o subtipo mais frequente deste cancro. Pouco se sabe sobre o impacto do vírus da imunodeficiência humana (VIH) nesta patologia. O principal objetivo deste estudo foi avaliar a associação entre CE e infeção pelo VIH. **Métodos:** Um estudo de caso-controlo foi conduzido, em 2018, no Hospital Central de Maputo, Moçambique (HCM). Adultos que consentiram em participar foram considerados elegíveis. Doentes com CCEE que realizaram teste de VIH constituíram o grupo de casos. Os controlos foram selecionados entre os doentes com condições benignas cirúrgicas que seriam operados no HCM, tendo sido emparelhados por sexo e idade. Os testes de qui-quadrado ou exato de Fisher foram utilizados para avaliar potenciais associações entre duas variáveis categóricas. Para realizar comparações entre grupos foi utilizado o teste t para amostras independentes ou o teste de Mann-Whitney para as variáveis contínuas. A razão de chances (OR) e o respetivo intervalo de confiança de 95% (IC) foram calculados usando regressão logística não-condicional. Um valor de p < 0,05 foi considerado significativo. **Resultados:** Durante o período de estudo, 92 casos e 92 controlos foram incluídos no estudo. 67,4% dos casos eram do sexo feminino. A idade mediana dos casos e dos controlos foi de 57 (35-83) e 52 (35-85) anos, respetivamente. O diagnóstico de VIH positivo aumentou significativamente as chances de desenvolver CE, principalmente nas mulheres (OR=4,81; IC 95%: 2,24–10,32; p<0,001), mas o mesmo não ocorreu nos homens (OR=2,26; IC 95%: 0,80–6,36; p=0,123). **Conclusão:** O cancro do esófago e o vírus da imunodeficiência humana são comuns em Moçambique. A infeção por VIH é um potencial fator de risco para CCEE, principalmente no sexo feminino. Pacientes com VIH e outros fatores de risco, como a exposição ao fumo doméstico ou do tabaco, devem ser educados e acompanhados para um diagnóstico precoce do cancro do esófago.

Palavras chave: *cancro do esófago, VIH, Moçambique.*

INTRODUCTION

Esophageal cancer (EC) is the eighth most common type of cancer worldwide and constitutes the sixth leading cause of cancer-related deaths[1]. The incidence of EC varies across regions and populations[2,3]. The age-standardized incidence rate was highest in Eastern and Southern Africa (8.3 and 7.4 per 100,000 persons-year, respectively). Differences in incidence rates were 56-fold between the country with the highest rate (Malawi, Southeastern Africa: 18.7), and the country with the lowest rate (Guinea, West Africa: 0.42)[1,4,5]. In 2018, EC was the fourth most frequent cancer and the fifth cause of cancer-related death in Mozambique, responsible for 597 and 459 new cases, in women and men, respectively, and 877 deaths[1]. Population-based data collected from two Mozambican registries, Maputo, and Beira, between 2015 and 2017, demonstrated a higher cumulative risk for esophageal cancer when compared with north and west African regions and US black populations. The cumulative risk of EC was 0.9% in Beira and 1.0% in Maputo[6]. People infected with human immunodeficiency virus (HIV) have a higher incidence of several malignancies compared with the general population[7]. Some studies suggest an increased risk of EC among people living with HIV infection[8,9,10]. A study conducted in Mozambique showed a high prevalence of HIV infection especially

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in females (15.1%) and the odds of getting infected with HIV were higher in older age groups and varied from 1.58 (95 % CI: 1.13-2.19) in age group 20-24 to 3.88 (95% CI: 2.56-5.89) in age 35-39[11]. However, there is no data regarding the prevalence of EC in Mozambique in both HIV-infected and HIV-uninfected patients, or if HIV is an associated risk factor for EC. The objective of the current study was to evaluate the association between HIV-positive tests and the incidence of EC.

METHODOLOGY

Study design and participants

A hospital-based case-control study was conducted at Maputo Central Hospital (MCH), in Maputo during 2018 (January first to December 31). MCH is the largest public and teaching hospital in Mozambique (1500 beds) and serves as a referral hospital for the entire country. The study was approved by the National Bioethics Committee of Mozambique (34/CNBS/2019), and the Human Research Protections Program of the University of California, San Diego, USA (UCSD IRB Approval –191187).

All adult EC patients attended at MCH during the study period were considered for enrollment. During the study period, 147 patients with EC were diagnosed, however, only 92 consecutive patients with EC with histological confirmation had an HIV test and were included in the study as cases. The histological diagnosis was reviewed for each case and confirmed by two pathologists. Hospital controls were identified from patients with a history of a non-malignant surgical condition, confirmed by histology, and had an HIV test. Cases and controls were matched for gender (1:1 for both males and females) and age (±10 years). Data were retrieved from the clinical files by a trained team. Data regarding HIV status was retrospectively collected from the hospital file registration in all series. Thus, 92 patients with EC and 92 controls were recruited. Consent for study participation was obtained from both cases and controls.

HIV Procedures

HIV testing was performed in parallel with two rapid HIV antibody detection kits (Determine [Abbott Laboratories] and Unigold [Trinity Biotech]). Cases and controls were classified as HIV-infected at cancer diagnosis based on a documented positive HIV antibody test, medical history indicating HIV infection, or an HIV clinic referral letter.

Data analysis

Variables collected were age at diagnosis, gender, race, pathological diagnosis, and HIV test result. For cases, data on employment status, place of residence and lifestyle habits as smoking and alcohol drinking were also collected. Statistical analysis was performed using R software v4.1.3. Categorical variables were summarized as frequencies and percentages. Continuous variables were presented as mean ± standard deviation (SD) or median, minimum, and maximum. Chi-square or Fisher's exact tests were used to evaluate the association between two categorical variables. Comparisons between groups were performed, using independent samples t-tests or Mann–Whitney tests for continuous variables. Odds Ratio (OR), and the corresponding 95% confidence interval (CI) were computed using non-conditional logistic regression. A p-value <0.05 was considered significant.

RESULTS

The characteristics of the 92 EC cases and the 92 controls are provided in Table 1 and Table 2,

Table 1 – **Characteristics of esophageal cancer group**

Characteristics	Total (n=92)	Female (n=62)	Male (n=30)	p-value
HIV				
Negative	33 (35.9%)	22 (35.5%)	11 (36.7%)	1.000
Positive	59 (64.1%)	40 (64.5%)	19 (63.3%)	
Age				
Mean ± SD	56.0 ± 10.1	56.8 ± 10.7	54.4 ± 8.8	0.268
Median (Min-Max)	57 (35-83)	57 (35-83)	53 (36-81)	0.268
Employment				
Domestic	76 (82.6%)	62 (100%)	14 (46.7%)	←0.001
Public servant	16 (17.4%)	0 (0%)	16 (53.3%)	
Place of residence				
Suburban	80 (87.0%)	58 (93.5%)	22 (73.3%)	0.017
Urban	12 (13.0%)	4 (6.5%)	8 (26.7%)	
Alcohol				
No	31 (33.7%)	24 (38.7%)	7 (23.3%)	0.220
Yes	61 (66.3%)	38 (61.3%)	23 (76.7%)	
Tabacco				
No	52 (56.5%)	36 (58.1%)	16 (53.3%)	0.838
Yes	40 (43.5%)	26 (41.9%)	14 (46.7%)	

Table 2 – **Characteristics of the control group**

Characteristics	Total (n=92)	Female (n=62)	Male (n=30)	p-value
HIV				
Negative	62 (67.4%)	45 (72.6%)	17 (56.7%)	0.197
Positive	30 (32.6%)	17 (27.4%)	13 (43.3%)	
Age				
Mean ± SD	54.1 ± 10.2	54.0 ± 10.8	54.2 ± 8.8	0.919
Median (min-max)	52 (35-85)	52 (35-85)	53 (36-81)	0.662
Surgical Pathology				
Abscess	2 (2.2%)	1 (1.6%)	1 (3.3%)	0.009
Goiter	15 (16.3%)	15 (24.2%)	0 (0%)	
Colostomy (benign)	2 (2.2%)	1 (1.6%)	1 (3.3%)	
Benign splenomegaly	3 (3.3%)	2 (3.2%)	1 (3.3%)	
Perianal fistula	10 (10.9%)	9 (14.5%)	1 (3.3%)	
Hemorrhoid	16 (17.4%)	8 (12.9%)	8 (26.7%)	
Hernia	31 (33.7%)	17 (27.4%)	14 (46.7%)	
Lymphadenitis	1 (1.1%)	1 (1.6%)	0 (0%)	
Lipoma	2 (2.2%)	2 (3.2%)	0 (0%)	
Proctitis	4 (4.3%)	3 (4.8%)	1 (3.3%)	
Benign cyst	4 (4.3%)	3 (4.8%)	1 (3.3%)	
Cholecystitis	1 (1.1%)	0 (0%)	1 (3.3%)	
Hidrocele	1 (1.1%)	0 (0%)	1 (3.3%)	

respectively. All cases and controls were black people. In the cases and controls most were female (67.4%). The mean age was 56.0 ± 10.1 years in cases and 54.1 ± 10.2 years in controls. All cases were ESCC. Regarding tumor location, the middle and lower third were more frequent (cervical:1; upper thoracic: 5, middle thoracic: 43; and lower thoracic: 43 cases). HIV positive test was identified in 59 (64.1%) cases, amongst them 67.8% were female and 32.2% were male. For the controls, 30 (32.6%) were HIV positive, 56.7% of these patients being female and 43.3% being male.

HIV (positive test) significantly increased the odds of developing EC, mainly in females (OR=4.81; 95% CI: 2.24–10.32; p<0.001), but the same did not occur in males (OR=2.26; 95% CI: 0.80–6.36; p=0.123) (Table 3 and Table 4).

In EC cases, all females were domestic (being continually exposed to smoke from burning wood for cooking), for the male gender, 46.7% were public servants and 53.3% did domestic affairs (including agricultural activity). Eighty-seven per cent of cases lived in suburban areas. The percentage of alcohol and smoking habits was 66.3% and 43.5%, respectively.

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Table 3 – **Characteristics of cancer cases and noncancer controls diagnosed at Maputo Central Hospital in Mozambique, 2018**

	Total (n=184)	Cases (n=92)	Controls (n=92)	p-value
Gender				
Female	124 (67.4%)	62 (67.4%)	62 (67.4%)	1.000
Male	60 (32.6%)	30 (32.6%)	30 (32.6%)	
Age				
Mean ± SD	55.0 ± 10.2	56.0 ± 10.1	54.1 ± 10.2	0.158
Median (min-max)	55 (35-85)	57 (35-83)	52 (35-85)	0.144
HIV				
Negative	95 (51.6%)	33 (35.9%)	62 (67.4%)	←0.001
Positive	89 (48.4%)	59 (64.1%)	30 (32.6%)	
HIV Negative				
Male	67 (70.5%)	22 (66.7%)	45 (72.6%)	0.715
Female	28 (29.5%)	11 (33.3%)	17 (27.4%)	
HIV Positive				
Male	57 (64.0%)	40 (67.8%)	17 (56.7%)	0.423
Female	32 (36.0%)	19 (32.2%)	13 (43.3%)	

Table 4 – **Risk factor analysis by gender and HIV**

Characteristics	OR	95% CI
HIV		
Negative	1	-
Positive	3.69	2.01-6.80
HIV (Females)		
Negative	1	-
Positive	4.81	2.24-10.32
HIV (Males)		
Negative	1	-
Positive	2.26	0.80-6.36

DISCUSSION

In this study, the overall estimated risk of developing EC was significantly higher in HIV-positive patients, particularly in females. To our knowledge, this is the first study to evaluate the association of HIV infection and the risk of EC, in Mozambique.

Come J et al. in 2018, studied a series of 522 consecutive patient cases of esophageal cancer and found that the median patient age was 56.1 years (range, 27 to 97 years), 55.7% were women and the majority were ESCC (12), these results were similar to what was found in our study, with a smaller series. Thrift AP et al. conducted a large retrospective cohort study to examine the risk of esophageal cancer among patients with HIV infection seen in the U.S. National Veterans Health Administration system reported higher crude rates of ESCC among male veterans with HIV infection compared with matched male veterans without HIV infection[14]. We found that the HIV positivity rate was significantly higher in the group with esophageal cancer, and it was associated with a significantly increased risk of EC mainly in females. These data agree with the work of Kayamba V et al. who concluded in a case-control study carried out in Zambia that HIV infection and domestic smoke exposure are risk factors for esophageal squamous cell carcinoma[9]. According to Ranjit S and Kumar S, HIV-infected smokers suffer more aggressive forms of cancer than non-smokers because of the cumulative effects of the virus and cigarette smoke carcinogens. The major types of cancer observed in HIV-infected smokers are lung, head and neck, esophageal, anal, and cervical cancers[15]. The study conducted by McCormack et al. mentioned an association of tobacco smoking with the risk of esophageal cancer (odds ratio [OR] = 2.6–8.0) in six sub-Saharan African countries, however, the HIV status was not assessed in most countries[16]. Moses et al. reported an OR of about 2.02 for smokers versus non-smokers for esophageal cancer in HIV-infected patients in Malawi[17]. Helleberg M et al. and Park LS

et al. found an association between esophageal cancer and smoking in the HIV population[18,19]. Of the 59 HIV-positive cases in our case series, 27 (45.8%) were smokers and 32 (54.2%) were non-smokers. Chronic exposure to cigarette smoke and/or domestic smoke in HIV carriers, who have immune deficits, may be responsible for esophageal carcinogenesis and for the high rate of squamous cell carcinoma in young HIV patients. This postulate needs to be confirmed and should be an alert for preventive measures in the HIV carrier community. Recently, a case-control study carried out in Mozambique, revealed that the occurrence of EC was strongly influenced by lifetime consumption of tobacco and alcohol, and hot tea drinking[13]. In our study, most of the EC patients come from suburban areas and have domestic activity, which is associated, in Mozambique, with the habit of cooking with charcoal or firewood[20]. However data on smoking or domestic smoke were not obtained in the contols, despite being questioned, which precludes a conclusion. According to Notor JJ et al. in Mozambique, the prevalence of HIV infection was higher in females (15.1%) than males (10.2%)[21]. The rate of HIV-positive controls, in our series, was higher in males. Men in Africa only seek medical care when they have an acute medical condition or a benign condition associated with important comorbidities such as HIV[22]. Although the selection of controls considered a pathology reported as a benign condition and the presence of HIV test, the fact that men, as mentioned above, generally go to the hospital for benign situations, if they are being followed for chronic pathologies or HIV, may have biased the sample and may be a reason for not finding a significant result as was verified in the female gender. However, this study suggests that HIV determines an increased risk of esophageal cancer in Mozambique as observed in other studies[23,24].

Limitations in this study

A relatively small sample size limited the generalizability of the findings. The study was conducted in a single hospital, which may not represent the broader population of Mozambique. Controls were selected from patients with non-malignant surgical conditions, which might not accurately represent the general population. Additionally, the higher rate of HIV-positive controls in males compared to the general population could have affected the results, particularly in the male subgroup analysis. The retrospective nature of the data collection could introduce biases due to missing or incomplete information. The reliance on hospital records for HIV status and other variables may not capture all relevant factors influencing EC risk. As the study was adjusted only for gender, there could be other unmeasured confounders such as dietary habits, environmental exposures, and socioeconomic status that might influence the association between HIV and EC. While the study identified smoking and alcohol use as risk factors, detailed quantitative data on these were not obtained, limiting the ability to assess their full impact on EC risk in conjunction with HIV infection). Besides, this information was missing in the control group. Finally, the findings may be influenced by specific geographic and cultural factors unique to the study location, which may not apply to other regions of Mozambique or different countries. However, the study found a significant association between HIV and EC in females but not in males, which may be due to gender differences in health-seeking behaviours or eventually other underlying biological mechanisms not explored in this study.

Despite these limitations, the study provides important insights into the relationship between HIV infection and esophageal cancer risk in Mozambique, underscoring the need for further research that mitigates the aforementioned limitations and public health interventions in this area.

CONCLUSION

This study demonstrates a significant association between HIV infection and an increased risk of

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developing esophageal cancer (EC) in Mozambique, particularly among females. The results show that HIV-positive individuals have higher odds of developing EC, with the risk being notably higher in women compared to men. This finding aligns with previous research conducted in other regions, suggesting that HIV infection may be a critical risk factor for EC. The study highlights the need for targeted preventive measures and early detection strategies for EC in HIV-infected populations, especially considering the high prevalence of HIV in Mozambique.

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Conflict of interest

The authors declare that they do not have competing interests.

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