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Original Research Article

The Pertinent Role of HSV and CMV in Sudanese Esophageal Cancer Epidemiology

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Abstract

Background: Viruses may play a role in the development of esophageal cancer (EC), although this is not yet known with certainty. This study, which examines Sudanese individuals with esophageal tumors, seeks to identify the involvement of cytomegalovirus (CMV) and herpes simplex virus (HSV) in the development of esophageal cancer. ***Materials and methods:*** This study looked back at 61 blocks of formalin-fixed, paraffin-embedded (FFPE) tissue that had already been identified as esophageal cancers. It used immunohistochemical staining to find herpes simplex virus type 1 and cytomegalovirus. Data were obtained from histopathology laboratories at the National Health Laboratory (NHL) and Soba University Hospital between January 2017 and January 2020. Positive results were confirmed with the polymerase chain reaction (PCR) technique. ***Results:*** Of the 61 FFPE blocks analyzed, 35 (57.4%) belonged to men. The bulk of participants (54.1%) were older than 60 years old. The most prevalent tumor type was squamous cell carcinoma (SCC), which accounted for 75.4% of cases. 16.4% of participants, equally divided between males and females, tested positive for HSV. 70% of HSV positive results came from people over the age of 60, and all of them were in SCC cases. Males accounted for 57% of the positive results. Individuals over the age of 60 were responsible for 80% of positive CMV results, while SCC cases accounted for 85%. All the PCR results were negative. ***Conclusion:*** These results imply a link between HSV, CMV, and esophageal cancer. We need more research with a larger sample size to understand how these viruses cause esophageal cancer.

Keywords: Esophageal cancer, Herpes simplex virus (HSV), Cytomegalovirus (CMV).

INTRODUCTION

In 2020, esophageal cancer, a malignant tumor in the digestive system, caused 0.6 million new cases and 0.54 million deaths worldwide, making it one of the leading causes of cancer-related mortality and a significant health concern worldwide [1]. It occupies the ninth ranking among all malignancies worldwide [2]. Esophageal squamous cell carcinoma (ESCC) is prevalent in the East, East Africa, and South America, where it accounts for 90% of all esophageal cancer cases worldwide. Esophageal adenocarcinoma carcinoma (EAC) is more prevalent in affluent countries than in impoverished countries [3]. In Africa Esophageal cancer (EC) is a significant cause of cancer morbidity and mortality in Sub-Saharan Africa, with disproportionately high rates of occurrence along the eastern corridor, which extends from Ethiopia to South Africa. Age-standardized incidence rates in Africa's high-risk corridor range from 9 to 47 cases per 100,000. In this region, EC is the third most common cause of cancer-related mortality. ESCC is the most prevalent histological subtype, accounting for more than 90% of all cases in Sub-Saharan Africa [4]. EC is the third most frequently treated disease at the Port Sudan Oncology Center in Sudan, following breast and prostate cancer [5]. It affects females (predominantly SCC, 89.2%) more than males (predominantly AC) and happens at a relatively young age [6]. A diverse array of malignant effects on the host's cellular DNA can result from viral replications. Approximately 20% of all human

oncogenesis is caused by oncoviruses, or cancer-causing viruses [7]. Esophageal cancer screening is likely to be essential in the future for the prevention and reduction of mortality, as it is occurring more frequently and acts quite aggressively [8]. In order to emphasize the circumstances in Sudan, EC is the fourth most prevalent among men and the fifth most prevalent among women. In clinical practice, the likelihood of developing EC is still influenced by environmental factors, including diet, dysplasia and tooth loss, smoking, age, sex, GERD, and genetics [9]. However, there is limited evidence, to the best of our understanding, that establishes a correlation between HSV-1 and CMV infections in patients with esophageal cancer.

MATERIALS AND METHODS

This study aimed to retrospectively screen for the presence of herpes simplex virus type 1 and cytomegalovirus in esophageal tumor tissue samples. Immunohistochemical staining methods, following standard procedures, were performed on a total of 61 Formalin-fixed, paraffin-embedded (FFPE) tissue blocks. The positive result slides were scratched and subjected to PCR analysis. The specimens were obtained from histopathology laboratories at the National Health Laboratory (NHL) and Soba University Hospital between January 2017 and January 2020.

Ethical Approval

The study protocol obtained permission from the ethical committee of Prof. Medical Research Consultancy Center.

Data analysis

The collected data was organized in a data sheet and subsequently inputted into a computer software called SPSS. The data was then analyzed to determine frequencies and cross-tabulations.

RESULTS

This study investigated 61 FFPE blocks that had previously been identified as esophageal tumors. Of these participants, 35 (57.4%) were males and 26 (42.6%) were females. HSV was found in 10 of the 61 subjects (16.4%), evenly distributed between males and females. CMV was discovered in 14 out of 61 patients, accounting for 22.9% of the total. Eight of these (57%) were men, while six (43%) were women. 33 of the 61 individuals (54.1%) were over the age of 60, with 21 of them (63.6%) being male. SCC is the most common tumor type, evenly distributed among boys and females, followed by Benign, AC, and Kaposi sarcoma, accounting for 46/61(75.4%), 9(14.8%), 5(8.2%), and 1(1.6%), respectively, as shown in Table 1 and Figure 1.

Table 1: Show the distributions of HSV (+ve/-ve), CMV(+ve/-ve), age, and tumor types throw the study subjects.

Variable	Males	Females	Total
HSV			
Positive	5	5	10
Negative	21	30	51
Total	26	35	61
CMV			
Positive	8	6	14
Negative	27	20	47
Total	35	26	61
Age			
<60	14	14	28
>60	21	12	33
Total	35	26	61
Tumor Types			
SCC	23	23	46
AC	5	0	5
Kaposi sarcoma	0	1	1
Benign	7	2	9
Total	35	26	61

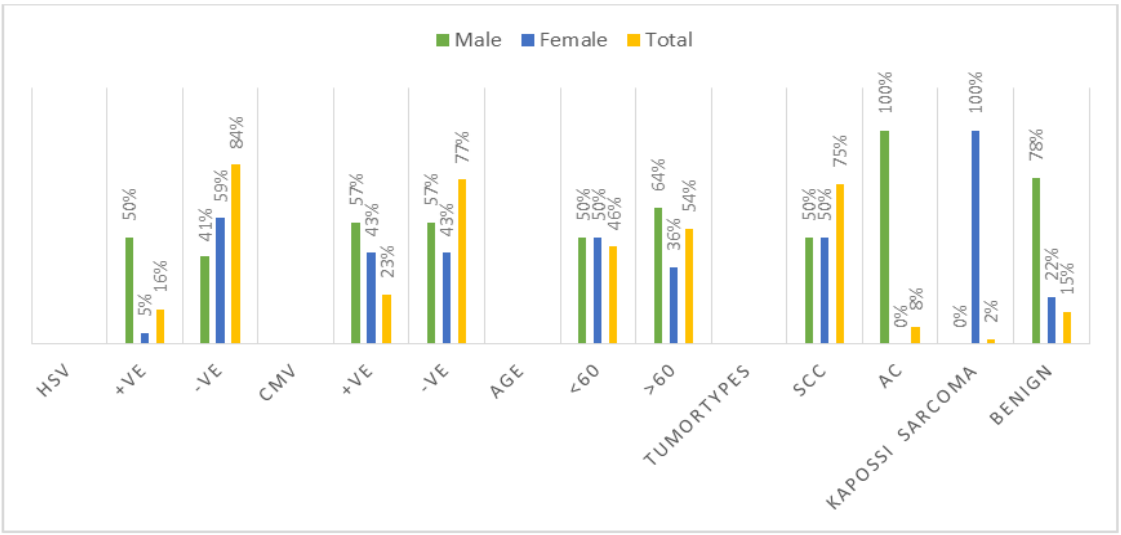

Figure 1: Show the distributions of HSV (+/-), CMV (+/-), age, and tumor types among the study subjects

Five out of 35 men (14%) and five out of 26 females (19%) tested positive for HSV. Age-wise, the over-60 age group identified 7 out of 10 (70%) of the HSV positive results, comprising a total of 33 patients (21%). Table 2 and Figure 2 reveal that all positive HSV results were of the SCC type.

Table 2: Distribution of HSV (positive or negative) by Sex, Age, and Tumor Types

Variable	HSV Positive	HSV Negative	Total
Males	5	30	35
Females	5	21	26
Total	10	51	61
Age			
<60 years	3	25	28
>60 years	7	26	33
Total	10	51	61
Tumor Types			
SCC	10	36	46
AC	0	5	5
Kapossi sarcoma	0	1	1
Benign	0	9	9
Total	10	51	61

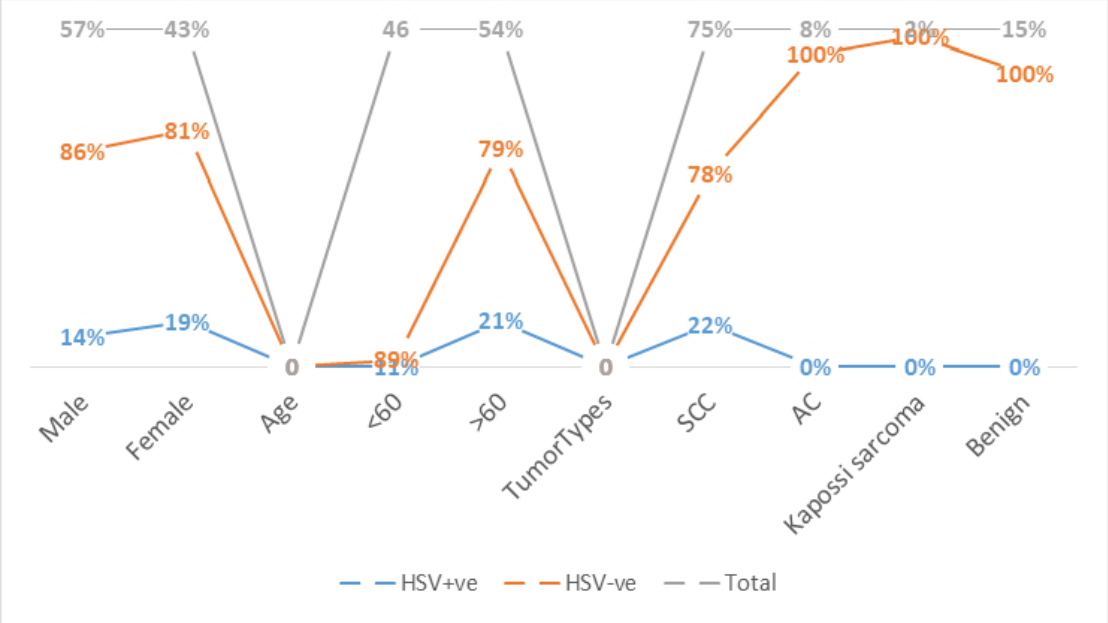

Figure 2: Distribution of HSV (positive or negative) by Sex, Age, and Tumor Types

We identified CMV in 14 out of 61 patients, representing 22.9% of the total. Of these, 8 out of 35 (23%) were men and 6 out of 26 (23% were women). This accounts for 6 out of 14 favorable outcomes (43%). Patients above the age of 60 discovered 8 out of 10 positive CMV results, accounting for 8 out of 33 (24%). When investigating different tumor types, the majority of positive CMV findings were discovered in SCC, followed by AC and Kaposi sarcoma, with 12 out of 14 (85.8%), 1 (7.1%), and 1 (7.1%), respectively, as shown in Table 3 and Figure 3.

Table 3: Distribution of CMV (positive or negative) by Sex, Age, and Tumor Types

Variable	CMV Positive	CMV Negative	Total
Males	8	27	35
Females	6	20	26
Total	14	47	61
Age			
<60 years	6	22	28
>60 years	8	25	33
Total	14	47	61

Variable	CMV Positive	CMV Negative	Total
Tumor Types			
SCC	12	36	48
AC	1	4	5
Kaposi sarcoma	1	0	1
Benign	0	7	7
Total	14	47	61

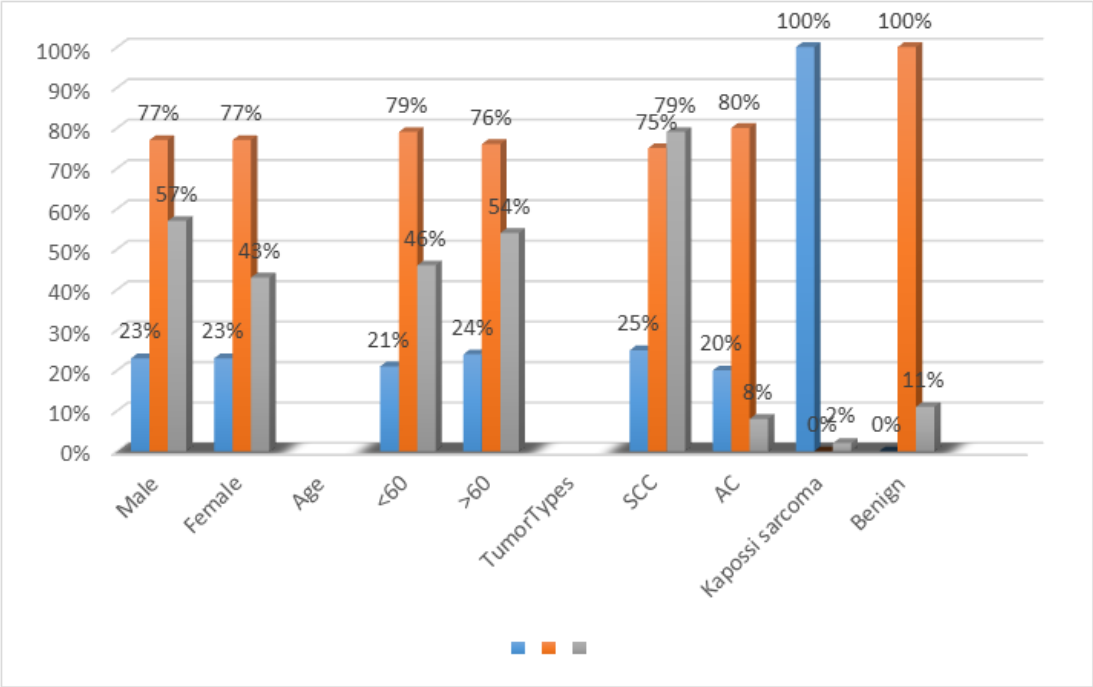

Figure 3: Distribution of CMV (Positive/Negative) by Sex, Age, and Tumor Types.

DISCUSSION

Esophageal cancer is a prevalent disease that affects people of all ages and genders, including those in Africa and Sudan. We still have much to learn about the origins of EC. There could be several risk factors contributing to the wide regional variations in EC occurrence. There is evidence to support the idea that contracting cancer-causing organisms can raise the likelihood of developing EC. There has been a longstanding belief that infection may contribute to the development of EC. For example, researchers discovered the first evidence of a connection between human papillomavirus (HPV) infection and ESCC in the early 1980s. Evidence suggests that HPV infection may contribute to the development of ESCC in certain high-risk populations, but a definitive link between infection and EC remains unestablished [10]. Our study revealed that a significant proportion of individuals affected by EC are male, with the ESCC type being the most common form. This finding aligns with previous studies conducted in Africa and Sudan [4, 9]. Researchers have identified certain species, including polyoma viruses, Epstein-Barr viruses, and human papillomavirus (HPV), as potentially having a direct impact on squamous cell carcinoma. It's worth mentioning that HPV is now associated with esophageal adenocarcinoma (EAC), although this connection is not apparent in the early stages of the disease. Instead, research has linked HPV33 to the development of dysplasia [11]. On the other hand, it is believed that HSV can infect the squamous lining of the esophagus, in addition to its regular infection of the squamous mucosa of the mouth and uterine cervix. In 1985, researchers made an interesting discovery when they found herpes virus particles in biopsy samples of esophageal carcinomas. Subsequent analysis showed the presence of DNA in 31.7% of the previously examined 164 surgical specimens for esophageal cancer. The histopathological investigation revealed HSV-positive instances in ESCC, which demonstrated significant differentiation. We found that the rates of infection with a combination of these three viruses in malignant mucosa exceeded 10.0% and exhibited a significant correlation with the pathological grade of EC (P = 0.001). A potential cause for EC could be infection with HPV-16, HSV-1, or EBV [12]. We found that both males and females, as well as individuals over 60 years old, equally distributed the positive samples of HSV in our study. We discovered CMV in 57% of males and 80% of individuals over 60 years old, which contradicts certain earlier studies that suggested esophageal cancer cases were more common in younger age groups [6]. The lack of preventive and surveillance programs explains the disparity in Sudan's situation. Thus, it is essential to

implement these programs and carry out additional research with a more extensive sample size to ascertain the impact of these viruses on the development of esophageal cancer. It is crucial to acknowledge that viruses play a significant role in about 20% of all human oncogenesis [7]. Despite the potential drawback of formalin fixative destroying the DNA of these viruses, it can lead to all PCR results being negative.

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