

HIV infection and esophageal cancer in Sub-Saharan Africa: a comprehensive meta-analysis

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Abstract

Africa hosts the highest burden of esophageal cancer (49%) and HIV (60%) worldwide. It is imperative to investigate the synergistic impact of these two diseases on African populations. This study conducted an exhaustive computerized search of databases, including Medline/PubMed, Embase, Web of Science, Scopus, Cochrane library, and African Journals Online, to identify eligible studies up to October 2023. HIV infection was the exposure, esophageal cancer risk was the outcome, and healthy subjects with no cancer history served as comparators. Study quality was assessed using the Newcastle-Ottawa scale, and potential publication bias was evaluated through funnel plots and the Egger test. Meta-analyses were conducted using Stata 17.0 software and involved a thorough examination of 98,397 studies. Out of these, eight studies originating from Eastern and Southern Africa, recognized as esophageal cancer hotspots on the continent, met the eligibility criteria. The analysis revealed a non-significant association between HIV infection and esophageal cancer risk (odds ratio = 1.34 [95% confidence interval, 0.85-2.12]; with 0.26 as p-value of overall effects). The Egger test yielded a p-value of 0.2413, suggesting the absence of publication bias. In summary, this systematic review and meta-analysis indicate that there is no established causal link between HIV infection and esophageal cancer risk. However, further research is essential to delve into the potential mechanisms underlying this relationship.

Keywords

HIV infection. Esophageal cancer. Sub-Saharan Africa. Systematic review. Meta-analysis.

Introduction

HIV stands as a persistent and formidable threat to global public health^{1,2}. In 2022, approximately 39 million individuals worldwide were living with HIV³. Yet, the greatest impact of this pandemic is felt on the African continent, which, in 2018, bore the burden of 25.7 million people living with HIV (PLHIV) and witnessed 470,000 AIDS related fatalities⁴. The East and Southern Africa subregions accounted for 20.3 mil-

lion PLHIV, while the North, West, and Central Africa sub-regions contributed 5.4 million to this statistic⁴. These staggering figures designate sub-Saharan Africa as the epicenter of the HIV epidemic, harboring 60% of global cases. Coincidentally, esophageal cancer has also found a stronghold in this region⁵, where it accounts for more than 40% of all cases worldwide⁶. Consequently, investigating the potential synergy between these two prevalent health challenges within the context of Africa is of paramount importance.

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Received in original form: 20-11-2023

Accepted in final form: 22-11-2023

DOI: 10.24875/AIDSRev.23000018

Recent years have seen a shift in the causes of mortality among PLHIV, with cancer emerging as a leading factor⁷⁻⁹. Notably, HIV infection has been identified as a risk factor for various cancers, including liver, stomach, anal cancers, and Kaposi's sarcoma^{10,11}. While the association between HIV infection and esophageal cancer has been established in the United States¹², findings in China have contradicted this link¹³. Yet, despite the coexistence of both diseases in Africa, no systematic review has comprehensively explored their relationship. Existing individual studies have primarily reported the frequency of HIV infection among individuals with esophageal cancer in Africa¹⁴⁻¹⁶, offering limited temporal and geographical scope, and a fragmented understanding of the connection between esophageal cancer and HIV infection on the continent. Hence, it is imperative to scrutinize the association between HIV infection and the risk of esophageal cancer in Africa, a step crucial for the development of targeted strategies aimed at preventing and controlling this devastating disease. This meta-analysis, conducted in this context, evaluates the impact of HIV infection on the etiology of esophageal cancer through case-control studies carried out in African populations.

Materials and methods

This systematic review and meta-analysis were conducted based on the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA)¹⁷. The review protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42023473775.

Eligibility criteria

The following eligibility criteria were used to identify the studies. Inclusion criteria: (1) observational studies comparing esophageal cancer risk between people with HIV/AIDS and uninfected controls or the general population. (2) All studies must contain available data reporting the relationship between HIV serology and esophageal cancer. (3) Studies must have been conducted on the African continent and involve human participants. Studies were excluded according to the following exclusion criteria: (1) unpublished articles; nonhuman research; anonymous reports; editorials, letters, commentaries, and reviews will be excluded from the study. (2) Studies that do not provide estimates of effect in the form of odds ratios, rate ratios, risk ratios, or relative risks, or that do not allow these values to be calculated, will also be excluded. (3) Studies whose

data are inaccessible, even after request to their authors, will also be excluded. (4) No sample size restrictions will be considered.

Data sources and search strategy

Databases such as Medline/PubMed, Excerpta Medica Database (Embase), Web of Science, Scopus, Cochrane Central, and African Journals Online (AJOL) were queried to identify pertinent electronic studies demonstrating the relationship between esophageal cancer and HIV infection in endemic areas of Africa up to September 2023. The search terms used in these six databases were "HIV infection" OR "Human Immunodeficiency Virus" OR "AIDS" OR "Acquired Immune Deficiency Syndrome" OR "Risks factors" AND "Esophageal Neoplasm" OR "Esophagus Neoplasm" OR "Esophagus Cancer" OR "Esophageal Cancer" OR "Esophageal malignancy" OR "Esophageal Squamous Cell Carcinoma" OR "Esophageal Adenocarcinoma" OR "EAC" OR "ESCC" and relevant synonyms and variations (Supplementary Table 1). These searches were then adjusted to the requirements of each specific database (i.e., the use of operators and symbols). A manual search in Google Scholar and a cross-search of the references cited in the retrieved studies was then carried out. No limits were established in terms of date of publication or language of publication.

Study selection

The identified studies were first exported to EndNote, where duplicates were removed, and then to Rayyan software to better organize the selection and review process¹⁸. The selection process is reported and structured according to the PRISMA flow diagram¹⁹. The authors initiated the selection process by independently evaluating the titles and abstracts of previously identified studies. Subsequently, a second independent selection was conducted by carefully examining the full text of articles that met the initial eligibility criteria, identifying those where eligibility remained unclear. Finally, the two authors rigorously and jointly assessed the eligibility of each study, particularly those with uncertain eligibility, to determine their inclusion in the systematic review and meta-analysis. The inclusion criteria encompassed observational studies involving residents of Africa, where HIV/AIDS infection served as either a primary or secondary risk factor for esophageal cancer. At each stage of study selection, any disparities were addressed through a consensus-seeking discussion before progressing to the next stage.

Data collection and quality assessment

For each study that met our eligibility criteria, comprehensive data were collected, including title, country, first author, publication date, number of cases of esophageal cancer, number of controls, HIV status, HIV diagnosis methods, collection period, data collection methods, study population, relative risk, and 95% confidence interval (CI), or odds ratio (OR) and 95% CI. In instances where comparative data were not available in the literature, they were calculated using appropriate statistical software. Study participants were categorized into two groups: those who had been infected by HIV and those who had not been infected by HIV. Studies conducted across multiple countries²⁰ were disaggregated by country, with the author's name duplicated and followed by the country's initials.

Quality assessment

The authors proceeded to independently assess the quality of the studies using the Newcastle-Ottawa Scale (NOS) tool for case-control studies. This assessment was based on the NOS's three dimensions: (I) selection of study groups; (II) comparability of the groups; and (III) assessment of outcomes²¹. The study quality classification system outlined by Stang was utilized for this study. As per this system, the highest possible NOS score is 9 points, with studies scoring 7-9 points being classified as high quality; those scoring 4-6 as moderate quality; and those scoring 0 to 3 as low quality²¹. Any disagreements between authors were resolved through consensus.

Publication bias assessment

The authors proceeded to independently assess possible publication bias was assessed by visual scrutiny of the funnel plot. Subsequently, the Egger regression test²² was employed to statistically assess any asymmetry detected in the funnel plot. Publication bias was acknowledged when the p-value falls below 0.10²³. Then, the trim-and-fill test was used to confirm that the asymmetry of the funnel diagram is not linked to the publication bias of the studies²⁴. Risk of bias assessment was performed using STATA version 17.0 (StataCorp LP, Texas) software for Windows.

Data synthesis and analysis

The qualitative analysis of the data was meticulously extracted from the included studies by GTK and EJN

and subjected to systematic analysis. The summarized outcomes of these analyses are presented in table 1. For quantitative synthesis, statistical analyses were conducted using the Stata software (version 17.0; StataCorp) for Windows. The pooled effect estimates and their corresponding 95% CI were calculated by the inverse variance method of DerSimonian and Laird²⁵. Dichotomous data relating to HIV and esophageal cancer were represented as odds ratios (OR) with corresponding 95% confidence intervals (95% CI) in a forest plot. We used a random-effects model to account for study heterogeneity. Heterogeneity among the included studies was assessed using the I^2 statistic, with significance set at $p < 0.05$, as described by Higgins and Thompson²⁶. An I^2 value between 75% and 100% denoted substantial heterogeneity. Differences between subgroups were assessed through visual inspection of confidence intervals and p-value of the overall association between HIV infection and esophageal cancer.

Results

Literature search results

The electronic yielded a total of 98,397 studies and manual searches have not provided any additional research. After eliminating duplicates (42,914 studies), a thorough review was conducted on 55,483 titles/abstracts. Following this review, 93 studies were selected for full-text examination. Subsequently, 85 studies were excluded for reasons such as non-alignment with the geographical focus of the study, comments, abstracts from conferences, studies presenting only the frequency of HIV among esophageal cancer patients, and inadequate data even after a request to the corresponding author. Finally, eight studies that fully met our inclusion criteria were selected for both qualitative and quantitative analysis (Fig. 1 and Table 1).

Study characteristics and quality assessment

The eight included studies, all case-control studies, encompassed a combined sample of 3490 individuals, consisting of 1639 cases, and 1851 controls or non-cancer individuals. These participants were sourced from five countries (Malawi, Zambia, Kenya, Tanzania, and Uganda) (Table 1) and belonging to the Eastern and Southern African sub-regions. The cases

Table 1. Characteristics of the different case-control studies included for meta-analysis

Author's (date)	Country	Study population	Cases/controls	HIV testing methods	Period of collect	Data collection methods	Type of study	NOS score
Asombang et al. (2016) ¹⁵	Zambia	Adults (≥ 18 years)	27/45	HIV test using ELISA	November 2010 and January 2012	Questionnaire	Case-control	6
Geßner et al. (2021) ²⁰	Malawi	Adults (≥ 22 years)	157/70	Serological status for HIV was determined using commercially available ELISAs; Enzygnost® HIV Integral II according to the manufacturer's protocol.	In 2010 and between 2014-2016	Questionnaire	Case-control	6
Kaimila et al. (2022) ²¹	Malawi	Adults (≥ 18 years)	300/300	HIV status was obtained from participant medical records (health passports). HIV testing facility was offered as per national guidelines.	Between 2017 and 2020	Interviewed using a structured questionnaire	Case-control	7
Kayamba et al. (2015) ²²	Zambia	Adults (≥ 18 years)	50/50	Later determination of the presence of HIV antibodies using ELISA	October 2013 to May 2014	Simple questionnaire	Case-control	6
Mlombe et al. (2015) ²⁷	Malawi	Adults (≥ 18 years)	96/180	Rapid HIV testing	From January 2011 to February 2013	Administration of questionnaire	Case-control	7
Mmbaga et al. (2021) ²³	Tanzania	Adults	471/471	HIV status was obtained from participant medical records (health passports).	Between 2013 and 2015	Administration of questionnaire	Case-control	7
Narh et al. (2021) ⁸	Kenya, Tanzania, and Malawi	Adults (≥ 18 years)	430/440 310/313 539/593	HIV status was obtained from participant medical records (health passports).	Between 2015-2018 in Kenya, 2015-2020 in Tanzania and 2017-2020 in Malawi	Administration of questionnaire	Case-control	7
Okello et al. (2016) ³²	Uganda	Adults (≥ 30 years)	67/142	HIV status was obtained from participant medical records (health passports).	From January 2003 to December 2014	Administration of the standardized questionnaire	Case-control	6

NOS: Newcastle-Ottawa scale; ELISA: enzyme-linked immunosorbent assay.

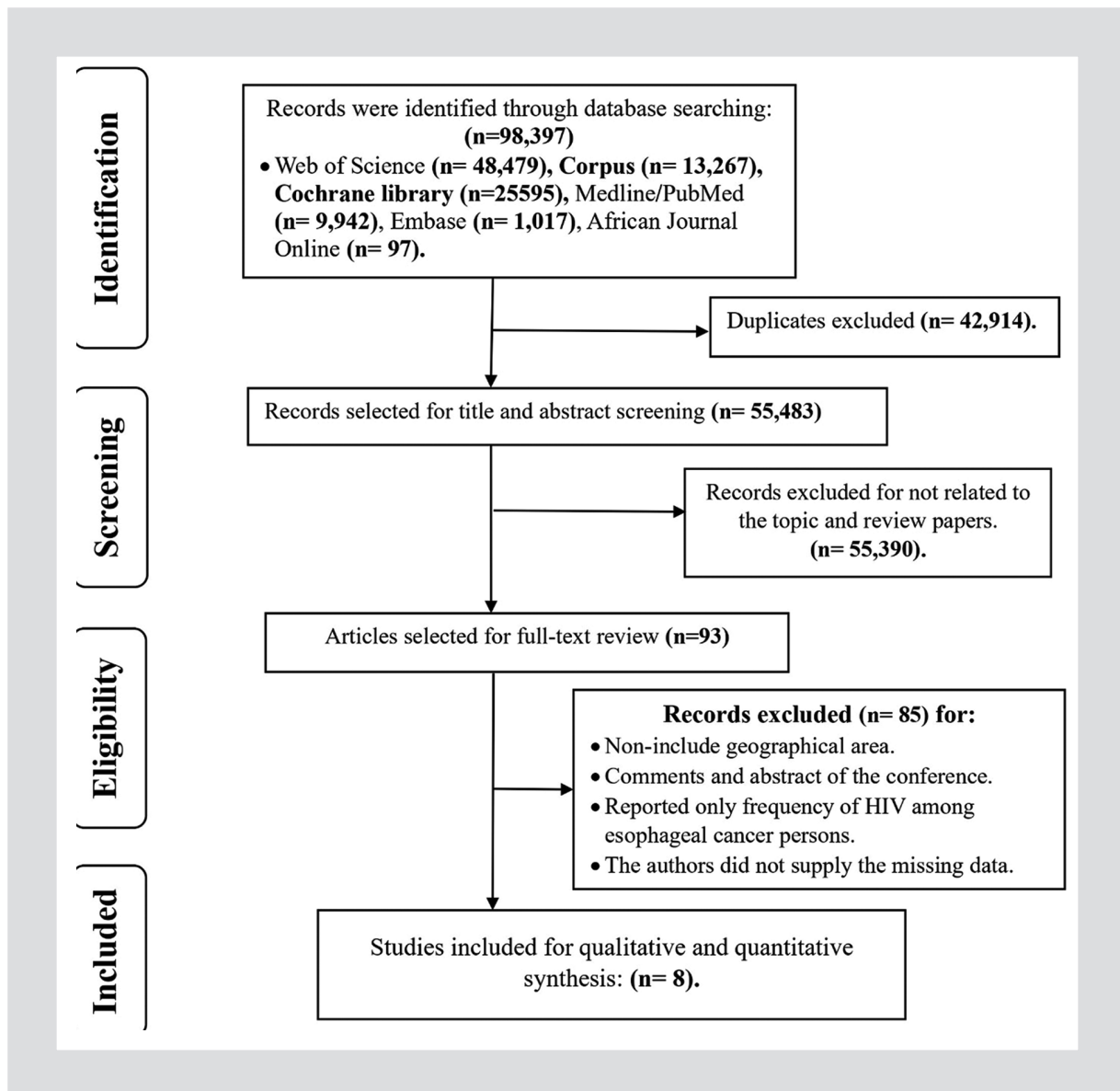


Figure 1. Schematic flow diagram for the selection of study included in the systematic review and meta-analysis.

comprised patients diagnosed endoscopically and confirmed either histologically, through computed tomography scans, or imaging (barium swallow) for esophageal cancer or those meeting clinical criteria for esophageal cancer. The control group comprised healthy volunteers recruited from the hospital setting with no family history or affiliation with any form of cancer. Patients were classified as HIV positive based on the data collected in their health record books (health passports), for those registered at the HIV care unit, or following confirmatory tests (rapid test, ELISA) for those who do not know their HIV status. Only the HIV serological status of participants was

addressed in these various studies. Data across these studies were primarily collected through questionnaires.

Meta-analysis of esophageal cancer risk in African population with HIV infection

The random-effects meta-analysis demonstrated risk of esophageal cancer is not statistically linked with HIV infection in sub-Saharan Africa. The pooled results reflected that there was no significant difference $OR = 1.34$ (95% CI, 0.85-2.12; $p = 0.21$), with significant heterogeneity ($p = 0.00$; $I^2 = 74.11\%$) (Fig. 2).

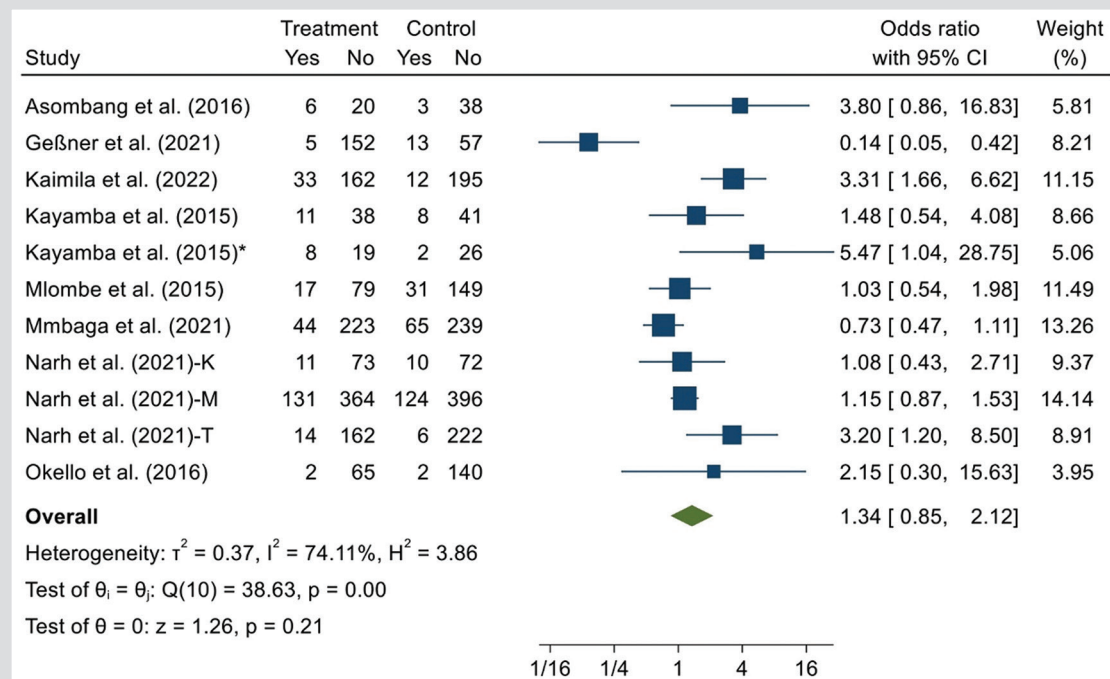


Figure 2. Meta-analysis forest plots illustrate the association between HIV infection and the risks of esophageal cancer. Data is presented as odds ratio with 95% confidence intervals utilizing a random-effects model. Heterogeneity among the studies was assessed using the I^2 statistic with a significance level of $p < 0.05$.

Assessment of small-study effects and publication bias

To assess the possibility of publication bias or other sources of effect on small studies, a funnel plot was produced (Fig. 3). Visual inspection of the funnel plot revealed an asymmetric distribution of study results (Fig. 3A). However, the Egger regression test for small-study effects did not detect a potential publication bias ($p = 0.2413$). However, the trim-and-fill analysis and the contoured funnel plot identified two missing studies for perfect funnel plot symmetry (Fig. 3B).

A funnel plot was generated to evaluate the potential presence of publication bias or other influences on smaller studies (Fig. 3). Visual scrutiny of the funnel plot exposed an asymmetrical distribution of study outcomes (Fig. 3A). Nonetheless, the Egger regression test, designed to detect small-study effects, did not reveal any significant indication of publication bias ($p = 0.2413$). In contrast, both the trim-and-fill analysis and the contoured funnel plot highlighted the absence of two studies required for achieving perfect symmetry in the funnel plot (Fig. 3B).

Discussion

Africa bears the highest global burden of both HIV infection and esophageal cancer, with South and Eastern Africa identified as high-endemic regions for these diseases, significantly impacting the well-being of the populations²⁻⁴. Understanding the association between HIV infection and the risk of esophageal cancer is crucial for tailoring targeted care to prevent and control this devastating disease. Our meta-analysis specifically investigated the impact of HIV infection on the etiology of esophageal cancer through case-control studies conducted in Africa.

Contrary to expectations, our findings indicate that HIV infection is not linked to an increased risk of esophageal cancer, aligning with the results reported by Geng et al.¹³ in China. Notably, disparities in results from studies in Africa, such as those in Zambia, Tanzania (limited to older subjects), and Malawi, reporting a significant association, highlight the potential influence of geographical variation and age. Moreover, variations in sample sizes, diagnostic methods, and antiretroviral

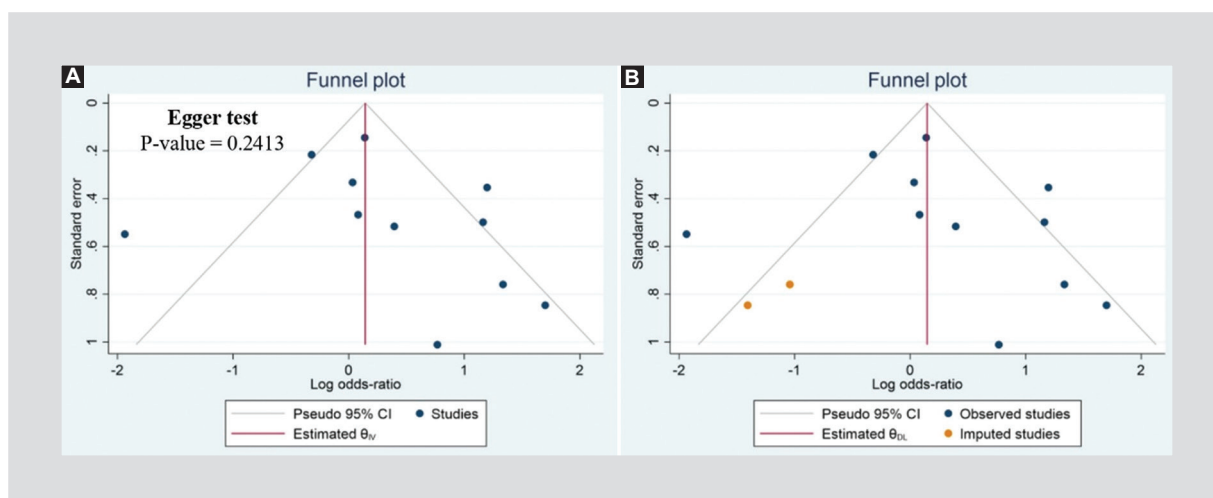


Figure 3. Funnel plots assessing the existence of publication bias. **A:** standard funnel plots, and p-value of regression-based egger test for small-study effects. **B:** funnel plots after trim and fill method.

treatments could contribute to the observed non-association. The provision of antiretrovirals to participants registered in HIV care units, helping to maintain normal CD₄ counts, might mitigate cancer risk, as CD₄ count decline is closely linked to cancer risk²⁷.

The absence of coinfection with oncogenic human viruses, such as hepatitis B and C, and high-risk human papillomaviruses, in HIV-positive patients could further explain the non-significant association^{14,28}. Another hypothesis suggests that genetic variability in the virus within Africa, compared to Europe and America, might play a role²⁹. Studies have indicated that certain HIV proteins with oncogenic potential are more prevalent in America and Europe, potentially rendering populations in these regions more susceptible to esophageal cancer³⁰⁻³⁵.

In conclusion, our meta-analysis indicates no significant association between HIV infection and the risk of esophageal cancer. However, this contradicts the work of Persson et al.³⁶ which suggests that HIV/AIDS infection increases the risk of stomach and esophageal cancer. Health authorities in African countries need to remain vigilant, considering the virus's mutational potential, which could unpredictably escalate the impact of this public health concern.

Conclusions

This systematic review and meta-analysis reveal no significant association between HIV infection and the risk of esophageal cancer in Africa, particularly within regions of high endemicity. Nevertheless, a vigilant

health monitoring system should be instituted at national and continental levels to track the trajectory of this disease. Future research endeavors are poised to delve into the genetic and molecular underpinnings of prevalence in these specific African regions, advancing our understanding of the nuanced dynamics between HIV infection and esophageal cancer on the continent.

Limitations

Limitations were encountered during the execution of this study. First, the relatively modest size of the study population constrained the precision of risk assessment. In addition, although all included studies originated from East and Southern Africa, the limited number of studies hindered a comprehensive country-specific stratification for a more nuanced analysis. Finally, the absence of data in the included studies prevented an exploration of associations between CD₄ levels, the duration of HIV disease, adherence to ARV treatment, and the risk of esophageal cancer in the African context. We hypothesize that a future study addressing these limitations comprehensively would yield a more robust association between HIV infection and the risk of esophageal cancer.

Acknowledgments

We would like to thank the librarian at Walter Sisulu University, who helped us develop the search strategies used to search for studies in the databases.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.23000018. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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