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Impact of traditional smoking patterns on esophageal cancer incidence in African populations: Systematic review and meta-analysis protocol

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Abstract:

Introduction and Aim: Africa alone accounts for almost 49% of positive cases of esophageal cancer worldwide. Despite being a well-known cause of cancer, the precise amount of tobacco use—including its type, mode, and intensity that contributes to the risk of esophageal cancer in African populations has not been thoroughly determined.

Methods and analysis: This protocol is written following recommendations from the PRISMA Protocols 2015 statement. All studies published before January 2024 was searched using comprehensive search strings through EMBASE, Medline/PubMed, Web of Science, Scopus, Cochrane Central, and African online journal databases that have reported the association between tobacco use and the risk of esophageal cancer in Africa. RevMan software was used to compute a pooled estimate using a random effects model. We will consider subgroup analysis and meta-regression for esophageal cancer, smoking patterns, geographic location, and study design type.

Ethics and dissemination: This study, based on published data, will inform policy, practice, and research by providing information on the role of smoking in the etiology of esophageal cancer among the African population. Summary tables of evidence from individual studies was used to present the findings. The systematic review's final report was presented at conferences, submitted to leading clinicians and other healthcare professionals in the National Health Service, and published in a peer-reviewed journal in the form of a scientific article. CRD42023453871 is the registration number of this review protocol.

Keywords: Esophageal Cancer; Traditional Tobacco; Africa; Systematic Review Protocol.

1. Introduction

The eighth most prevalent disease globally and the sixth largest cause of cancer-related mortality is esophageal cancer (EC) [1]. Its prevalence has increased dramatically worldwide in recent years. According to the GLOBOCAN 2020 report, there were 0.6 million new cases and 0.54 million deaths worldwide in 2020 [2]. GLOBOCAN 2020 predictions for EC estimate approximately 739,666 new cases and 723,466 deaths in 2030, and 987,723 new cases and 914,304 deaths worldwide in 2040 if no action is taken [2]. The progression of this malignant tumor is significantly high in less developed regions in general, accounting for 80% of cases [3], particularly in Africa, where around 49% of cases are recorded worldwide [4]. This disease poses a significant challenge for health authorities in African countries.

Globally, observational studies have identified lifestyle variables including alcohol intake, food, tobacco use, and obesity have been linked to an elevated risk of EC. However, smoking is one of the main risk factors for EC in many countries and, combined with alcohol intake, accounts for approximately 90% of the population attributable fraction [5]. Nevertheless, the role of smoking remains highly controversial in several parts of the world [6]. Some studies have reported that smoking

slightly affects the risk of esophageal cancer, with a relative risk of around 1.4 times [7, 8]. Other studies have shown that regular smokers have a 2.5 to 4 times greater relative risk of esophageal cancer than people who have never smoked [9, 10]. Although smoking is a well-known risk factor in the development of esophageal cancer, its association varies from one continent to another. In Africa, since the work of Sambaing et al. (2019), which briefly assessed the effect of tobacco on the risk of esophageal cancer [11]. New studies have been published and new evidence has emerged on previous controversial factors for which there was insufficient power to demonstrate an effect. Additionally, the magnitude of the contribution of smoking type and intensity to the disease will also be elucidated alongside smoking status through a wider range of analytical methods aimed at filling potential gaps in the evidence. Especially in this African context, where cultural diversity and poverty have resulted in a variety of smoking methods and substances, which are often unknown due to their complex composition. The link between smoking habits and esophageal cancer becomes more difficult to determine due to this diversity. It would therefore be good to carve out the different smoking methods available in Africa, to compare them and find out which one might

have the lowest risk of esophageal cancer. This study aims to complete prior systematic reviews by adopting an updated approach that will employ a broader search strategy, include more databases and recent articles, and provide a more current synthesis of the issue. Hence, the present work aims to systematically review the published literature on the link between smoking and the risk of developing EC in Africa and to statistically synthesize the evidence supporting the strength of the relationship.

Research Objectives

The objective of this study is to procure a dependable estimation of the link between smoking patterns, types and intensities, and the risk of EC in the African population.

2. Methods

2.1. Registration and reporting results

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement's recommendations, as stated in [12], have been followed in writing this protocol. The results were presented following the guidelines stipulated by the PRISMA statement [13]. The registration number for this systematic review in PROSPERO is CRD42023453871.

Review Question

This review of studies published prior to August 2023, will seek to address the following question:

- What is the extent of the relationships between smoking patterns and EC risk in the African population?
- What is the impact of smoking modes on the occurrence of EC in Africa?
- What is the impact of smoking duration and frequency of consumption of different types of smoked substances on the etiology of EC in Africa?

Eligibility criteria

Articles will undergo review and selection for full-text analysis if they satisfy the following selection criteria: (1) The study must have been conducted in Africa; (2) It should be an observational study (cohort, case-control, cross-sectional) that describes and evaluates the strength of the link between tobacco consumption and the risk of esophageal cancer; (3) Studies should present data as odds ratios (OR), relative risks (RR), or hazard ratios (HR); (4) Studies involving only adult human

participants was considered. There were no limitations on language or sample size.

Studies was excluded for any of the following reasons: Studies that fail to establish a connection between smoking and esophageal cancer; anonymous reports, editorials, letters, commentaries, and reviews. Additionally, a study will not be included if it does not allow

the computation of these values or if it does not provide effect estimates in the form of odds ratios, rate ratios, risk ratios, or relative risks. Studies for which data remains inaccessible even after author inquiries will also be omitted. In cases of duplicate studies, only the most comprehensive and up-to-date version was considered. PICOS criteria for eligible studies are given in **Table 1**.

Table 1. PICOS for study eligibility criteria.

	Inclusion	Exclusion
Populations/participants	<ul style="list-style-type: none"> • Populations from African countries • Adults only (aged ≥ 18 years) 	<ul style="list-style-type: none"> • Children and adolescents (aged < 18 years) • Animals • Studies involving populations outside Africa
Interventions/exposure	<ul style="list-style-type: none"> • Smoking status (current smoker) • Smoking modes (commercial cigarettes; hand-rolled cigarettes and pipe) to see which type is more at risk. • Daily smoking intensities • Smoking duration 	<ul style="list-style-type: none"> • Studies that did not report any of the Interventions/exposure • studies in which the following parameters are associated with diseases other than oesophageal cancer
Comparators/Comparison	<ul style="list-style-type: none"> • Healthy Non-smokers without a family history of cancer 	<ul style="list-style-type: none"> • Healthy subjects with a family history of cancer
Outcomes:	<ul style="list-style-type: none"> • Risk of oesophageal cancer. 	<ul style="list-style-type: none"> • Studies that did not report this outcome
Study designs	<ul style="list-style-type: none"> • Cohort studies (prospective and retrospective) • Case-control studies • Cross-sectional 	<ul style="list-style-type: none"> • Review papers • Comments • Conference abstract • Unpublish paper

2.2. Data Source and Search Strategy

Databases including Medline/PubMed, Excerpta Medica Database (Embase), Web of Science, Scopus, Cochrane Central, and African Journals Online will serve as the primary sources for article searches. No historical time constraints (date of publication), and even less

the language of publication, was considered during searches. The terms outlined in Table 1 was applied for preliminary searches across Medline/PubMed databases (Table 2). Subsequently, searches were modified following the specifications (symbols and operators) of each unique database. Authors was reached to

provide missing information; conference abstracts and reviews of grey literature will also be considered. All pertinent abstracts from the aforementioned sources was scrutinized, and full papers was downloaded from databases or journal platforms. The references of these articles were meticulously examined to identify potentially suitable studies, the eligibility of which will then be assessed.

Table 2. Preliminary search strategy in Medline/PubMed database.

Search Number	Search detail
#1	"tobacco"[tiab] OR "tobacco use"[tiab] OR "tobacco smoke"[tiab] OR "smoke"[tiab] OR "smoking"[Mesh] OR "Marijuana smoking"[Mesh] OR "Cigarette"[Mesh] OR "commercial Cigarette"[Mesh] OR "hand-rolled Cigarette"[Mesh] OR "Cigar"[tiab] OR "pipe smoke"[tiab] OR "risk factor"[tiab] OR "tobacco smoke"[tiab]
#2	"Esophageal cancer"[MeSH] OR "Esophageal carcinoma"[tiab] OR "Oesophageal cancer"[tiab] OR "Esophageal tumor"[tiab] OR "Oesophageal tumor"[tiab] OR "Esophagus cancer"[tiab] OR "Oesophagus cancer"[tiab] OR "Esophageal Squamous-Cell Carcinoma"[tiab] OR "Esophageal Adenocarcinoma"[tiab] OR "ESCC"[tiab] OR "esophageal Neoplasms"[MeSH]
#3	"Africa" [MeSH] OR "East Africa"[tiab] OR "West Africa"[tiab] OR "Southern Africa"[tiab] OR "North Africa"[tiab] OR "Algeria"[tiab] OR "Angola"[tiab] OR "Benin"[tiab] OR "Botswana"[tiab] OR "Burkina Faso"[tiab] OR "Burundi"[tiab] OR "Cameroon"[tiab] OR "Cabo Verde"[tiab] OR "Cape Verde"[tiab] OR "Central African Republic"[tiab] OR "Chad"[tiab] OR "Comoros"[tiab] OR "Congo"[tiab] OR "Cote d'Ivoire"[tiab] OR "Djibouti"[tiab] OR "Egypt"[tiab] OR "Democratic Republic of Congo"[tiab] OR "Equatorial Guinea"[tiab] OR "Eritrea"[tiab] OR "Eswatini"[tiab] OR "Swaziland"[tiab] OR "Ethiopia"[tiab] OR "Gabon"[tiab] OR "Gambia"[tiab] OR "Ghana"[tiab] OR "Guinea"[tiab] OR "Guinea Bissau"[tiab] OR "Kenya"[tiab] OR "Lesotho"[tiab] OR "Liberia"[tiab] OR "Libya"[tiab] OR "Madagascar"[tiab] OR "Malawi"[tiab] OR "Mali"[tiab] OR "Mauritania"[tiab] OR "Mauritius"[tiab] OR "Morocco"[tiab] OR "Mozambique"[tiab] OR "Namibia"[tiab] OR "Niger"[tiab] OR "Nigeria"[tiab] OR "Rwanda"[tiab] OR "Sao Tome and Principe"[tiab] OR "Senegal"[tiab] OR "Seychelle"[tiab] OR "Sierra Leone"[tiab] OR "Somali"[tiab] OR "South African"[tiab] OR "South Africa"[tiab] OR "South African"[tiab] OR "Sudan"[tiab] OR "North Sudan"[tiab] OR "South Sudan"[tiab] OR "Tanzania"[tiab] OR "Togo"[tiab] OR "Tunisia"[tiab] OR "Uganda"[tiab] OR "Zambia"[tiab] OR "Zimbabwe"[tiab]
#4	#1 AND #2
#5	#1 AND #2 AND #3

2.3. Study selection

Full-text studies was chosen and validated for inclusion through the efforts of two independent reviewers. Disagreements was settled by dialogue among these reviewers. A

third reviewer will step in to determine eligibility and approve the final list of retained research if an agreement cannot be achieved. A PRISMA flow diagram (Figure 1) was

employed to visually elucidate the study selection process.

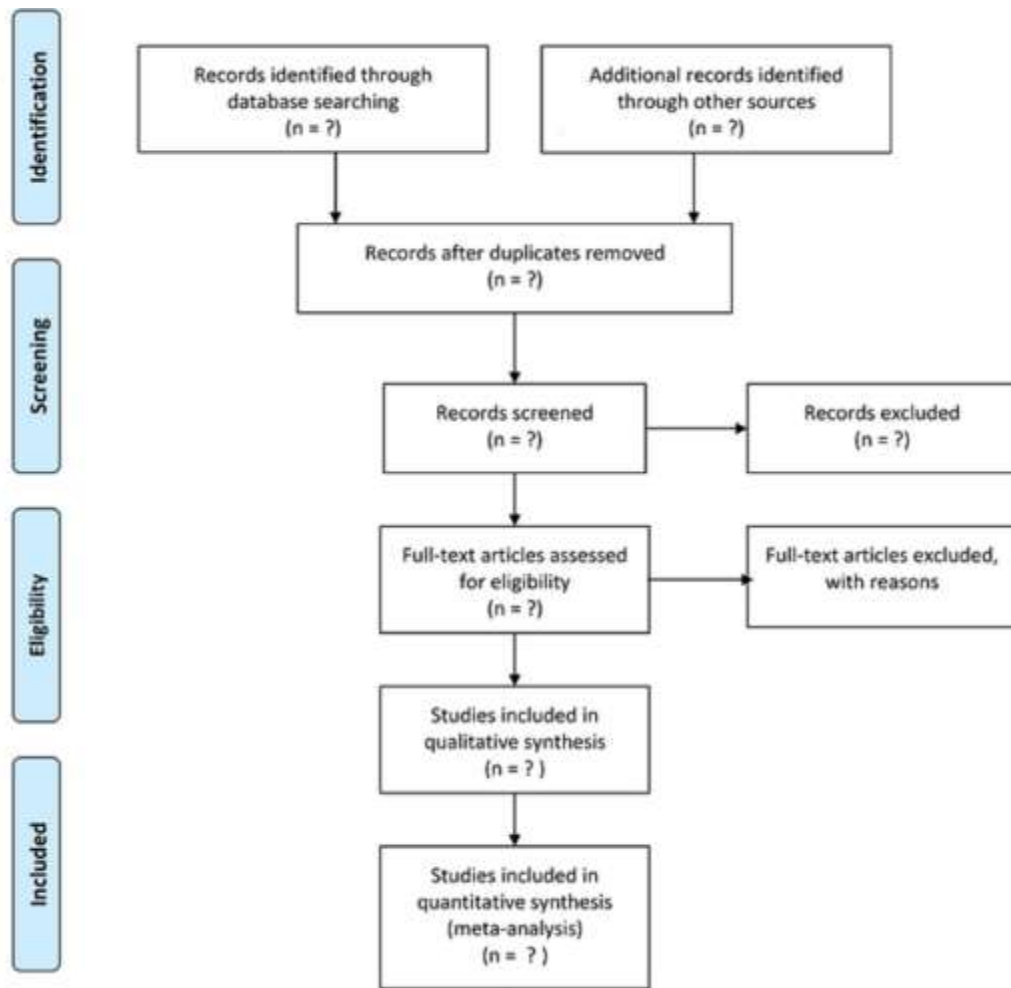


Figure 1. PRISMA flow diagram for study selection.

2.4. Data extraction and management

Duplicate results were eliminated after exporting the search results to EndNote, and then to the Rayyan software to better organize the selection and review process. For each study meeting our eligibility criteria, details such as authors' names, publication year, country, study design, study population, sample size, gender

distribution, type of smoked substance (cigarette commercial, pipe, hand-rolled cigarettes, etc.), smoking status or daily quantity smoked, adjustment for potential confounders, P-value, and effect sizes along with their corresponding 95% confidence intervals was meticulously extracted by two independent researchers employing a predefined extraction structure

form. In the event of any discrepancies, a process of mutual discussion was initiated, and if disagreements persist, a third impartial evaluator was consulted.

2.5. Quality assessment of studies

A system of nine scores based on the Newcastle Ottawa Scale (NOS) for case-control and cohort studies [14] and the Agency for Healthcare Research and Quality (AHRQ) instrument for cross-sectional studies [15] was used to comprehensively evaluate the quality of the included research. Every study was evaluated independently by the authors. Disagreements was settled by dialogue among these reviewers. Studies with a score greater than or equal to 7, out of a maximum of 9 points, was considered as high-quality studies and those with a score between 4 and 6 was considered as intermediate quality studies. However, studies with a score of less than 4 was considered low quality and was excluded from the study.

2.6. Risk of bias assessment

Possible publication bias was assessed via visual scrutiny of the funnel plot. Subsequently, any asymmetry seen in the funnel plot was statistically evaluated using the Egger regression test [16]. Publication bias was acknowledged when the P-value falls below 0.10 [17]. The Trim-and-Fill approach

recommended by Duval and Tweedie was used if publication bias is demonstrated [18]. The STATA 17.0 software for Windows (StataCorp LP, Texas) was used to perform the risk of bias.

2.7. Statistical analysis and data synthesis

A summary table and a forest plot diagram were used to display the features of the included research. Statistical analyses will then be conducted using Review Manager (RevMan) for Windows. In cases where enough studies or data are available, the I2 statistic, as defined by Higgins and Thompson [19], was used to assess heterogeneity between incorporated studies, with an I2 value of 75% to 100% indicating substantial heterogeneity. Should there be low variability between studies, a meta-analysis was performed to calculate a pooled estimate. Conversely, if data pooling is infeasible due to heterogeneity, we will descriptively present the outcomes of each study. The odds ratio will serve as the overarching metric to express the relationship between smoking and esophageal cancer. Subgroup analyses and meta-regressions was undertaken, exploring among participants categories such as smoking status, geographic distribution of studies; smoking modes (modern commercial cigarettes; hand-rolled cigarettes, and pipe), daily smoking intensities, smoking type, smoking duration, age, sex, and study design. The results will then be written up and

presented for publication following PRISMA guidelines.

In cases where a meta-analysis is not feasible, a narrative synthesis was undertaken, adhering to the guidelines as outlined by Popay et al. (2006) [20]. Finally, the results was meticulously documented and presented for publication following PRISMA guidelines [21]. This comprehensive approach will ensure the rigor, transparency, and reliability of our research findings.

The GRADE approach was employed by the authors to assess the quality of the evidence [22]. Three criteria: large effect, dose-response gradient, and opposing confounding was used to upgrade confidence in effect estimates, while five criteria: risk of bias, inconsistency, imprecision, indirectness, and publication bias was used to downgrade the quality of the evidence [23]. The different evidence bodies were handled following the Cuello-Garcia et al. (2022) scale [24].

3. Discussion

The incidence of esophageal cancer is on the rise globally. Conventional risk factors such as diet, HIV status, alcohol consumption, and smoking have been frequently cited in independent studies with varying degrees of

significance [25]. The discrepancies observed in multiple studies [7-10] conducted worldwide clearly highlight that the link between smoking and the risk of esophageal cancer fluctuates across different regions and countries. While often highlighted as a major risk factor in numerous observational studies conducted in Africa [8, 26, 27], these studies have not yielded consistent evidence on a continental scale. Hence, this systematic review and meta-analysis aim to provide a consolidated estimation of the risk of esophageal cancer development in individuals who smoke within the African context.

Conclusion

We hypothesize a strong correlation between smoking and the vulnerability to EC development in the African setting, given the increasing prevalence of EC worldwide, which has a significant impact in Africa. Upon the conclusion of this study, our objective is to furnish precise data concerning the tangible role of smoking in esophageal cancer risk. Such insights will empower the formulation of effective policies aimed at curbing the advancement of this disease. Furthermore, this research has the potential to pinpoint gaps in current knowledge and unresolved challenges, which could serve as foundational points for subsequent investigations. These future studies

may enhance our comprehension of the genuine influence of smoking on the etiology of

esophageal cancer in Africa.

Ethical considerations: This study does not require ethical approval or informed permission since it is a protocol for a systematic review and meta-analysis that primarily uses existing data and does not include patient participation.

Authors' Contributions: The authors (GTK and EJM) participated in the design, production, validation and editing of this work. They also read and approved the published version of the manuscript.

Conflicts of interests: The authors declare that they have no conflicts of interest.

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