



Esophageal cancer male to female incidence ratios in Africa: A systematic review and meta-analysis of geographic, time and age trends

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ABSTRACT

Esophageal squamous cell carcinoma (ESCC) remains the predominant histological subtype of esophageal cancer (EC) in many transitioning countries, with an enigmatic and geographically distinct etiology, and consistently elevated incidence rates in many Eastern and Southern African countries. To gain epidemiological insights into ESCC patterns across the continent, we conducted a systematic review and meta-analysis of male-to-female (M:F) sex ratios of EC age-standardised (world) incidence rates in Africa according to geography, time and age at diagnosis. Data from 197 populations in 36 countries were included in the analysis, based on data from cancer registries included in IARC's *Cancer Incidence in Five Continents*, *Cancer in Africa* and *Cancer in Sub-Saharan Africa* reports, alongside a systematic search of peer-reviewed literature. A consistent male excess in incidence rates overall (1.7; 95% CI: 1.4, 2.0), and in the high-risk Eastern (1.6; 95% CI: 1.4, 1.8) and Southern (1.8; 95% CI: 1.5, 2.0) African regions was observed. Within the latter two regions, there was a male excess evident in 30–39 year olds that was not observed in low-risk regions. Despite possible referral biases affecting the interpretability of the M:F ratios in place and time, the high degree of heterogeneity in ESCC incidence implies a large fraction of the disease is preventable, and directs research enquiries to elucidate early-age exposures among young men in Africa.

Abbreviations: AC, adenocarcinoma; AFCRN, African Cancer Registry Network; ASR, age-standardised rate; CI, confidence interval; CI5, Cancer Incidence in Five Continents (publication series/data source); CIA, Cancer in Africa (publication/data source); CISSA, Cancer in Sub-Saharan Africa (publication/data source); EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; IARC, International Agency for Research on Cancer; IRR, incidence rate ratio; M:F, male-to-female; PAH, polycyclic aromatic hydrocarbon; PBCR, population-based cancer registry; UN, United Nations

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1. Introduction

Esophageal cancer (EC) is the 8th most common cancer worldwide and is ranked 6th for cancer-related mortality [1]. The dominant histological subtype of EC worldwide is esophageal squamous cell carcinoma (ESCC), followed by adenocarcinoma (AC) [2]. Incidence rates of ESCC display marked geographic variation worldwide, with notably high incidence occurring in certain regions within countries in South America (e.g. Brazil), Asia (e.g. China and Iran) and Southern and Eastern Africa – the focus of this paper – where incidence rates are 20-fold higher than in West Africa [3]. In this African EC corridor of high risk, ESCC accounts for 94% of EC cases [2] and is the 2nd most common cancer in some populations e.g. in Malawian males [4], where age-standardised (world) incidence rates (ASR) are over 30 per 100,000. The diagnosis of ESCC often occurs at late-stage following the onset of dysphagia. Prognosis is extremely poor, thus the identification of risk factors and primary prevention strategies are a priority for reducing the burden [5].

Few etiologic studies of ESCC have been conducted in Africa relative to other high incidence regions worldwide, and as a consequence, the epidemiology of the disease in endemic regions remains poorly understood. Nevertheless, several well-established ESCC carcinogens including tobacco and alcohol consumption are likely to partially explain the elevated incidence [5,6] and studies thereof are underway. Etiological clues can be additionally gained from descriptive studies of ESCC in Africa, including investigating differences in incidence between the sexes, as has been conducted for other cancers [7–9]. Establishing the presence or absence of a sex differential in different African settings could provide clues as to the nature of contributing risk factors, i.e. whether gender-associated behaviours and exposures are likely to be implicated. While gender differences in certain exposures are unclear in sub-Saharan Africa (e.g. gender-specific patterns of dietary intake are not well described), it is evident that several potential contributors, e.g. tobacco and alcohol use, are more prevalent among males [10]. Further, a stand-out feature of the East African ESCC burden is the unusually high number of young (aged < 40 years old) patients [11]. Investigating whether a sex difference is evident in these young age groups, and at what age it manifests, will be of particular value in pointing to potential contributions of early life exposures and inherited susceptibility.

We therefore aimed in this study to examine sex differentials in incidence rates of EC across Africa. Using data from cancer registries included in IARC's *Cancer Incidence in Five Continents* (CI5), *Cancer in Africa* (CIA) and *Cancer in Sub-Saharan Africa* (CISSA) reports, alongside a systematic search of peer-reviewed literature, we explored variations by country, region, over time and by age, with a focus on high-risk regions in Eastern and Southern Africa.

2. Material and methods

We undertook a systematic review and meta-analysis of published data, reports and studies from which sex ratios (male-to-female) for EC incidence in Africa could be estimated for individual study 'populations' unique in place, calendar year and population group (e.g. ethnicity). Note: we refer to the ratio of male to female incidence rates as *sex ratios* as per the reporting of incidence data by biological sex, but use them as a tool to investigate gender-associated behaviours and exposures, rather than sex-linked biological risk factors – see [12].

2.1. Data sources and inclusion criteria

EC incidence sex ratios were estimated for populations satisfying the following criteria: (i) located in mainland countries within the United Nations (UN) demarcation of Africa; (ii) adult populations aged 20 years and over; (iii) indigenous African populations (predominantly or exclusively). Initially, no restrictions on year of diagnosis were applied.

Three data sources were used. Age and sex-specific EC (ICD-10 C15) incidence data were extracted from the CI5 series of volumes [13] a compendium of high quality cancer incidence based on submissions from population-based cancer registries (PBCR) at the national or subnational level, that is, in volumes for which African data were compiled.

Additional age- and sex-specific incidence data were sourced from the *Cancer in Africa* (CIA) [14] and *Cancer in Sub-Saharan Africa* (CISSA) (in-press), which captures incidence data from population-based cancer registries in Africa who are part of the African Cancer Registry Network (AFCRN). Finally, a systematic review of peer-reviewed literature was conducted using the following databases: Medline via Ovid, Google Scholar, Embase, Global Health, African Journals Online and BHOI-INCTR Cancer Control Library using the following terms: *esophag* OR oesophag*, cancer OR neopl* OR tumour OR carcin* OR malig*, Africa OR Sub-Saharan OR country name* (listed individually, including historical names e.g. Rhodesia). No lower date restrictions were imposed and studies published before August 2017 were included. Manuscripts were excluded if they did not include sex-specific incidence counts, were occupational cohorts or used sampling designs that were suggestive of deliberately modifying sex distributions. To avoid duplication due to the many journal articles presenting registry data, studies that overlapped with CI5 or the CIA/CISSA data, based on population group, place and date of diagnosis ranges, were excluded and CI5/CIA/CISSA data were retained.

Most data sources either did not report on EC histological types separately (ESCC vs AC) or the percentage of morphological verification was low, which prevented us from performing analyses on histologically verified ESCC. Estimates from a previous study [2] which reported the global incidence of EC by histological subtype were examined and the mean ESCC proportion for Africa was 93%. Therefore, we deemed this a negligible limitation.

2.2. Data extraction

From each source and for each population, we extracted the following data: country; location; derived UN geographic region in 2017; source or study design (population-based cancer registry (PBCR), other registry, case series, cases from case-control studies or cohorts); male, female and total number of EC cases; male, female and combined ASR; person-years or population size; calendar year and age group of diagnosis.

2.3. Statistical analysis

For each population, estimated sex incidence rate ratios (IRRs) of EC, defined as ratios of EC cancer incidence rates between sexes (male-to-female), were calculated by fitting Poisson regression models on EC counts, with a log offset of person-years if available or population data from censuses if not, with covariates included for sex and, if available, age (20–29 years, 30–39, 40–49, 50–59, 60–69, and 70+). The adjusted IRR was then estimated as $\exp(\beta_{\text{sex}})$. Studies that had no population data available were modelled in a similar fashion, but without a log offset, to produce a count ratio as an estimate of the sex IRR. To examine the comparability of sex count ratios and of sex IRRs, we also calculated count ratios for the latter and compared these ratios to the known IRR. The mean ratio of count ratio to IRR was 1.02 and the correlation was strong (Spearman's rank correlation coefficient $\rho = 0.91$, Fig. S1 in Supporting information) suggesting that count ratios could be used as good proxy of IRRs when population size is missing. Throughout, populations with no EC cases for both males and females did not contribute. If there were zero cases in either sex, they were also excluded if the total number of cases was less than five, and if five or more, zero events were censored with the value of 0.5.

Country-specific sex ratios were estimated by performing a random effects meta-analysis of each country's population-specific estimates

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