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

Article *in* Cancer Epidemiology · February 2018

DOI: 10.1016/j.canep.2018.01.020

CITATIONS
25

READS
401

24 authors, including:

Daniel Middleton
Queen's University Belfast
49 PUBLICATIONS **481** CITATIONS
SEE PROFILE

Rachel Hanisch
National Institutes of Health
12 PUBLICATIONS **250** CITATIONS
SEE PROFILE

Freddie Bray
International Agency for Research on Cancer
324 PUBLICATIONS **234,101** CITATIONS
SEE PROFILE

Charles Dzamalala
University of Malawi
37 PUBLICATIONS **824** CITATIONS
SEE PROFILE

Author manuscript as accepted by: *Cancer Epidemiology*

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

Daniel R. S. Middleton[a], Liacine Bouaoun[a], Rachel Hanisch[a], Freddie Bray[b], Charles Dzamalala[c], Steady Chasimpha[c], Diana Menya[d], Charles Gombé Mbalawa[e], Guy N'Da[f], Mathewos A. Woldegeorgis[g], Ramou Njie[h], Moussa Koulibaly[i], Nathan Buziba[j], Josefo Ferro[k], Hassan Nouhou[l], Femi Ogunbiyi[m], Henry R. Wabinga[n], Eric Chokunonga[o], Margaret Z. Borok[o], Anne R. Korir[p], Amos O. Mwasamwaja[q], Blandina T. Mmbaga[q], Joachim Schüz[a] and Valerie A. McCormack[a]

[a] Section of Environment and Radiation, International Agency for Research on Cancer (IARC), Lyon, France

[b] Section of Cancer Surveillance, International Agency for Research on Cancer (IARC), Lyon, France

[c] Malawi Cancer Registry, Queen Elizabeth Central Hospital, Blantyre, Malawi

[d] School of Public Health, Moi University, Eldoret, Kenya

[e] Registre des Cancers de Brazzaville, Sce de Carcinologie et Radiothérapie, CHU de Brazzaville, Brazzaville, Congo

[f] Registre de Cancer d'Abidjan, Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire

[g] Addis Ababa City Cancer Registry, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia

[h] GNCR, The Gambia Hepatitis Intervention Study, International Agency for Research on Cancer, c/o MRC unit, The Gambia

[i] Registre de Cancer de Guinée, Université de Conakry, Conakry, Guinea

[j] Eldoret Cancer Registry, Moi University School of Medicine, Eldoret, Kenya

[k] Beira Cancer Registry, Hospital Central da Beira, Beira, Mozambique

[l] Registre des Cancers du Niger, Laboratoire d'Anatomie et Cytologie Pathologiques, Faculté des Sciences de la Santé, Niamey, Niger

[m] Ibadan Cancer Registry, Department of Pathology, University College Hospital, Ibadan, Nigeria

[n] Kampala Cancer Registry, Department of Pathology, College of Health Sciences, Makerere University, Kampala, Uganda

[o] Zimbabwe National Cancer Registry, Parirenyatwa Hospital, Harare, Zimbabwe

[p] Nairobi Cancer Registry, Kenya Medical Research Institute, Centre for Clinical Research, Nairobi, Kenya

[q] Kilimanjaro Christian Medial Centre, Moshi, Tanzania

Correspondence to: **Daniel R. S. Middleton**, Section of Environment and Radiation, IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France, Tel: +33 472 738 566, E-mail: middletond@fellows.iarc.fr

Abbreviations used:
AC – adenocarcinoma
AFCRN – African Cancer Registry Network
ASR – age-standardized 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

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.

Keywords: esophageal cancer, sex ratios, Africa, meta-analysis, systematic review

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 (CISAA)* (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 $\exp(\beta_{sex})$. 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 $\rho = 0.91$, Figure 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 (derived as above) and presented on a forest plot. Heterogeneity across studies/populations was tested using the I-squared (I^2) statistic, which estimates the percentage (0 to 100%) of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no heterogeneity, and larger values show increasing heterogeneity. Meta-analyses were presented according to broad region and overall EC incidence: high incidence (Eastern Africa); high incidence (Southern Africa) and low incidence. "High incidence" refers to those countries where either male or female ASRs were greater than their respective world mean (male: 9.0; female: 3.1) according to GLOBOCAN 2012 estimates. While GLOBOCAN estimates don't permit a robust

demarcation of a high incidence region, based on the above criteria, the following countries were categorised as high incidence: Malawi, Uganda, Kenya, South Africa, Tanzania, Mozambique, Zimbabwe, Zambia, Swaziland, Ethiopia and Sudan. The other countries that meet the criteria, but did not contribute to this analysis are Lesotho, Burundi, Botswana, Comoros, South Sudan, Somalia, Madagascar, Rwanda, Angola, Djibouti and Eritrea.

Age group-specific EC sex IRRs were also estimated using a Poisson regression stratified by age group (with the same age groups as above) and were then used in a meta-analysis by regions based on geography and incidence. In the event that a provided age group overlapped two age groups, the upper age category was assumed, e.g. age stratum 25-34 were categorised in the 30-39 as older EC patients are more common.

To interpret results in the context of the world EC scenario, African sex IRRs were compared with those estimated from CI5 volume X registries, ensuring no overlapping populations. Sex IRRs and absolute male excesses were plotted against female EC ASRs, taken from the present analysis where available and GLOBCAN 2012 estimates were substituted in their absence.

Statistical analyses were performed using R, version 3.3.1, [15] and p-values lower than 0.05 were considered statistically significant.

3. Results

3.1 Studies and data included

A flow chart of data inclusion in the different analytical components is presented in Figure 1.

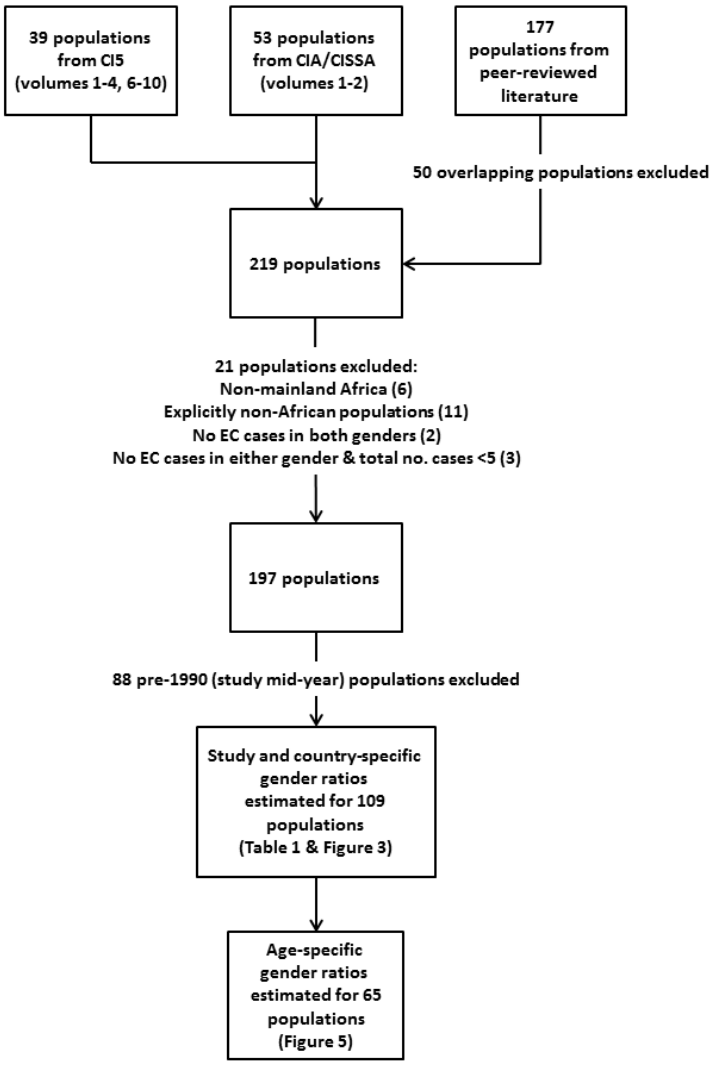

Figure 1 Flow diagram of population inclusion in the different analytical components of the study. Population refers to a group of individuals sharing a common location, period of diagnosis and ethnicity.

After exclusions, EC incidence data for 35 populations from 13 African countries were included from CI5 (4,791 EC cases), including 4 from the EC high incidence corridor (i.e. countries with a male or female ASR greater than its global average): Malawi, South Africa, Uganda and Zimbabwe. CIA/CISSA data contributed a further 41 populations from 22 countries (15,669 EC cases), including from 12 countries not reported in CI5. A systematic review of peer-reviewed literature yielded 121 eligible populations from 25 countries (25,035 EC cases), including data from 11 additional countries to CI5 or CIA/CISSA. Fifty (28%)

literature studies initially identified (177 populations) were excluded due to duplication. From all sources, a total of 197 populations from 36 of the 49 UN mainland African member states met the inclusion criteria and were retained for analysis – resulting in a sample size of 45,495 EC cases: 29,828 in men and 15,667 in women. The vast majority of cases were from countries in the Eastern (27%) and Southern African (61%) regions.

3.2 Temporal variation in EC sex ratios

Overall, 11% of M:F ratios were <1, 36% were between 1 to <2, 27% were between 2 to <4 and 26% were 4% or over. Plotting ratios by time, a strong negative trend was observed (Figure 2). In particular, pre-1990 ratios from Eastern and Southern Africa were much higher and have substantially declined. Some estimates [16] had over 30 men, whilst no female EC cases were present. Due to this temporal trend, all pre-1990s data were excluded from further analyses (88 populations). Studies reporting data from before 1990 and the ratios calculated using them are presented in Table S1 for reference (supporting information).

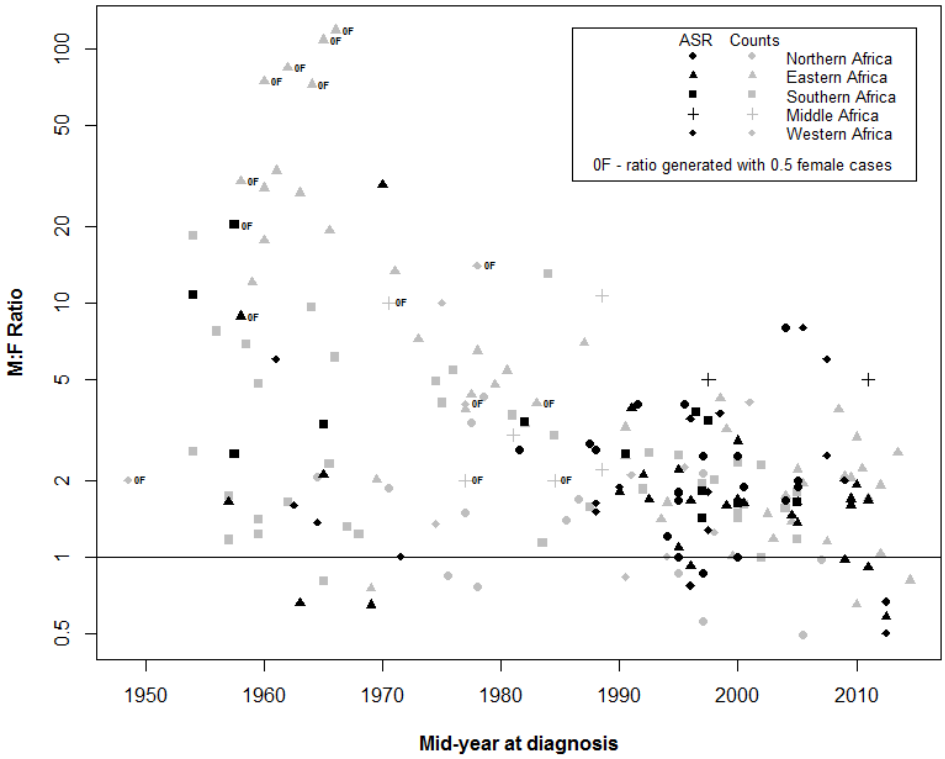

Figure 2 Male-to-female esophageal cancer incidence ratios (y-axis displayed in log scale) plotted against the mid-year of diagnosis, estimated by IRRs (black points) or count ratios (grey points).

3.3 Geographic variation in EC sex ratios

The sex ratios, calculated for each individual study, that were used to generate country-specific estimates are presented in Table 1 and are organised by UN geographic region and country. Country and region-specific (revised regions based on EC incidence) sex ratios for 27 countries are displayed in the forest plot in Figure 3. All estimates are age-adjusted, except for four countries (Morocco, Sudan, Zambia and Togo).

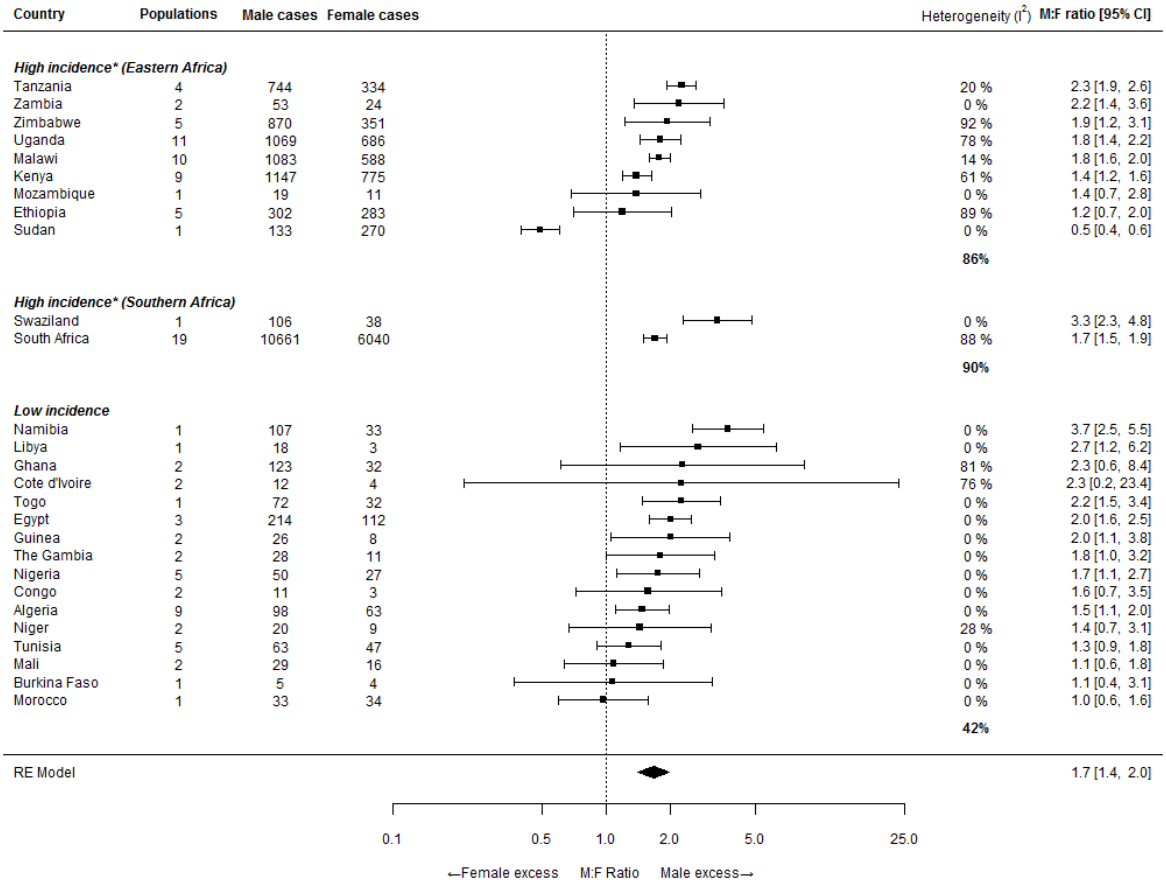

Figure 3 Forest plot of country and region-specific sex ratios estimated using random effects models. Point estimates and their corresponding populations and diagnosis periods are shown in Table 1. *High incidence denotes countries for which the male or female EC ASR exceeds the global EC incidence rate in GLOBOCAN.

Table 1 Study/population-specific sex ratios estimated using Poisson regression. *Study designs: 1 = registry data; 2 = case series; 3 = case-control study.

First author (year)	Data source	Location	Year at diagnosis	Study design *	M:F ratio	Male cases (ASR, where available)	Female cases (ASR, where available)	Total cases
			Northern Africa					
Algeria								
IARC (1997)	CI5 (vol. VII)	Setif	1990-1993	1	2.03	9 (1.2)	4 (0.3)	13
Meguenni (1998)[14]	Literature	Tlemcen	1994-1996	2	0.86	6	7	13
IARC (2002)	CI5 (vol. VIII)	Algiers	1993-1997	1	1.77	34 (0.9)	19 (0.5)	53
IARC (2003)	CIA	Batna	1995-1999	1	0.70	5	9	14
IARC (2003)	CIA	Constantine	1994-1997	1	1.50	3 (0.4)	1 (0.1)	4
IARC (2003)	CIA	Oran	1996-1998	1	2.09	17 (1.5)	8 (0.6)	25
IARC (2003)	CIA	Setif	1993-1997	1	1.73	9 (0.5)	5 (0.3)	14
IARC (2007)	CI5 (vol. IX)	Setif	1998-2002	1	0.84	3 (0.2)	4 (0.2)	7
IARC (2013)	CI5 (vol. X)	Setif	2003-2007	1	1.64	12 (0.4)	6 (0.2)	18
Egypt								
Bahnassy (2005)[17]	Literature	Cairo	1996-1998	2	2.13	34	16	50
IARC (2007)	CI5 (vol. IX)	Gharbiah	1999-2002	1	1.99	70 (1.7)	40 (0.9)	110
IARC (2013)	CI5 (vol. X)	Gharbiah	2003-2007	1	1.99	110 (1.7)	56 (0.9)	166
Libya								
IARC (2013)	CI5 (vol. X)	Benghazi	2003-2005	1	2.70	18 (1.6)	3 (0.2)	21
Morocco								
Chbani (2012)[18]	Literature	Fez	2004-2010	2	0.97	33	34	67

Sudan								
Gasmelseed (2015)[19]	Literature	Gezira state	1999-2012	2	0.49	133	270	403
Tunisia								
IARC (2003)	CIA	Sousse	1993-1997	1	1.02	3 (0.4)	3 (0.4)	6
IARC (2003)	CIA	Tunis	1994	1	1.10	18 (1.2)	16 (1.0)	34
IARC (2003)	CIA	Sfax	1997	1	1.10	2 (0.6)	2 (0.7)	4
IARC (2007)	CI5 (vol. IX)	Sousse	1998-2002	1	1.61	5 (0.5)	2 (0.2)	7
IARC (2013)	CI5 (vol. X)	North	2003-2005	1	1.40	35 (0.5)	24 (0.3)	59
Total cases (Northern Africa)						***559***	***529***	***1088***
			Eastern Africa					
Ethiopia								
Ali (1998)[20]	Literature	Addia Ababa	1992-1996	2	1.63	88	54	142
Ashine & Lemma (1999)[21]	Literature	Sidama	1986-1995	2	3.23	42	13	55
Shewaye & Seme (2016)[22]	Literature	Addis Ababa	2014-2015	3	0.81	96	119	215
Leon (2017) [23]	Literature	Addis Ababa	2012-2012	3	1.03	37	36	73
IARC (In press)	CIA	Addis Ababa	2012-2013	1	0.65	39 (2.2)	61 (3.8)	100
Kenya								
White (2002)[24]	Literature	Tenwek	1989-1998	2	1.40	160	114	274
IARC (2003)	CIA	Eldoret	1998-2000	1	1.62	89 (24.5)	51 (15.5)	140
Lodenyo (2005)[25]	Literature	Nairobi	1998-2001	2	1.00	34	34	68
Ogendo (2007)[26]	Literature	Nairobi	2001-2005	2	1.17	32	27	59
Dawsey (2010)[11]	Literature	Tenwek (<30 year olds)	1996-2009	2	1.48	65	44	109
Parker (2011)[27]	Literature	Tenwek	1999-2009	3	1.74	177	102	279
Patel (2013)[28]	Literature	Eldoret	2003-2006	3	1.37	92	67	159
IARC (In press)	CIA	Eldoret	2008-2011	1	1.79	220 (28.5)	122 (16.9)	342
IARC (In press)	CIA	Nairobi	2007-2011	1	1.00	278 (12.1)	214 (12.5)	492
Malawi								
Banda (2001)[29]	Literature	Blantyre district	1994-1998	1	2.11	148 (15.4)	70 (9.3)	218
IARC (2003)	CIA	Blantyre	2000-2001	1	1.80	65 (17.4)	31 (10.7)	96

Crofts (2008)[30]	Literature	Blantyre	2007-2008	2	1.14	24	21	45
Mothes (2009)[31]	Literature	Zomba	2004-2006	2	2.20	83	38	121
Gyorki (2012)[32]	Literature	Lilongwe	2005-2006	2	1.94	33	17	50
Wolf (2012)[33]	Literature	Lilongwe	2008-2010	2	2.08	183	88	271
IARC (2013)	CI5 (vol. X)	Blantyre	2003-2007	1	1.61	320 (37.6)	182 (23)	502
Mtonga (2013)[34]	Literature	Blantyre	2010	2	0.65	11	17	28
Mlombe (2015)[35]	Literature	Lilongwe & Blantyre	2011-2013	3	1.91	63	33	96
IARC (In press)	CIA	Blantyre	2009-2010	1	1.66	153 (30.8)	91 (19.3)	244
Mozambique								
IARC (In press)	CIA	Beira	2009-2013	1	1.39	19 (5.5)	11 (3.3)	30
Tanzania								
IARC (2003)	CIA	Dar es Salaam	1990-1991	1	2.63	60	23	83
IARC (2003)	CIA	Kilimanjaro	1998-2000	1	3.33	76	22	98
Mchembe (2013)[36]	Literature	Mwanza & Dar es Salaam	2008-2013	2	2.22	226	102	328
Gabel (2016)[37]	Literature	Dar es Salaam	2006-2013	2	2.04	382	187	569
Uganda								
Wabinga (1993)	Literature	Kyadondo county	1989-1991	1	1.65	43 (13.0)	26 (7.2)	69
IARC (1997)	CI5 (vol. VII)	Kampala	1991-1993	1	1.84	63 (18.2)	36 (8.7)	99
Wabinga (2000)	Literature	Kyadondo county	1991-1994	1	1.51	83 (15.8)	55 (9.4)	138
Wabinga (2000)	Literature	Kyadondo county	1995-1997	1	1.08	68 (13.0)	63 (14.2)	131
IARC (2002)	CI5 (vol. VIII)	Kampala	1993-1997	1	1.16	104 (13.2)	91 (12.2)	195
IARC (2003)	CIA	Mbarara	1997-2000	1	4.25	42	9	51
IARC (2007)	CI5 (vol. IX)	Kampala	1998-2002	1	1.76	121 (14.1)	77 (8.4)	198
IARC (2013)	CI5 (vol. X)	Kyadondo county	2003-2007	1	1.47	157 (15.6)	125 (11.5)	282
Alema & Iva (2014)[38]	Literature	Northern Uganda	2009-2011	2	2.86	53	18	71
Okello (2016)[39]	Literature	Mbarara	2003-2014	3	3.79	53	14	67
IARC (In press)	CIA	Kyadondo county	2008-2012	1	1.92	282 (22.6)	172 (11.8)	454
Zambia								
Kayamba (2015)[40]	Literature	Lusaka	2013-2014	3	2.57	36	14	50

Asombang (2016)[41]	Literature	Lusaka	2010-2012	3	1.70	17	10	27
Zimbabwe								
IARC (1997)	CI5 (vol. VII)	Harare	1990-1992	1	3.68	153 (29.5)	22 (7.7)	175
IARC (2002)	CI5 (vol. VIII)	Harare	1993-1997	1	2.23	220 (19.3)	65 (8.8)	285
IARC (2007)	CI5 (vol. IX)	Harare	1998-2002	1	2.57	191 (15.1)	57 (5.3)	248
IARC (2013)	CI5 (vol. X)	Harare	2003-2006	1	1.49	181 (22.2)	99 (15.3)	280
IARC (In press)	CIA	Harare	2010-2012	1	0.93	125 (14.6)	108 (16.1)	233
Total cases (Eastern Africa)						***5287***	***3052***	***8339***
			Southern Africa					
Namibia								
IARC (2003)	CIA		1995-1998	1	3.73	107 (6.3)	33 (1.7)	140
South Africa								
Levy (1998)[42]	Literature	Soweto	1998	3	2.00	26	13	39
Dietzsch (2002)[43]	Literature	Cape Town	2002	3	2.30	23	10	33
Pacella-Norman (2002)[44]	Literature	Johannesburg	1995-1999	3	1.93	267	138	405
IARC (2003)	CIA		1989-1992	1	2.49	6592 (23.1)	2990 (9.1)	9582
IARC (2003)	CIA	Elim	1991-1994	1	2.41	41	16	57
IARC (2003)	CIA	Transkei region	1996-1998	1	1.34	134 (37.5)	173 (26.5)	307
IARC (2003)	CIA	Transkei region	1996-1998	1	1.64	117 (62.5)	97 (34.5)	214
Dlamini (2005)[45]	Literature	Kwazulu Natal	2005	2	1.17	47	40	87
Dandara (2006)[46]	Literature	Western Cape province	1997-2003	3	1.42	85	60	145
Matsha (2006)[47]	Literature	Transkei region	2003-2005	2	1.54	142	92	234
Li (2008)[48]	Literature	Cape Town	1997-2003	4	1.47	84	57	141
Van der Merwe (2010)[49]	Literature	Free State province	1995	2	2.51	158	63	221
Van der Merwe (2010)[49]	Literature	Free State province	2000	2	2.34	103	44	147
Van der Merwe (2010)[49]	Literature	Free State province	2005	2	1.79	68	38	106
Somdyala (2010)[50]	Literature	Eastern Cape province	1998-2002	1	0.93	444 (32.7)	479 (20.2)	923
Sitas (2012)[51]	Literature	Johannesburg	1995-2006	2	1.60	429	268	697
IARC (2013)	CI5 (vol. X)	Eastern Cape province	2003-2007	1	1.62	475 (32.0)	533 (19.6)	1008

Sewram (2014)[52]	Literature	Eastern Cape province	2001-2003	3	0.99	334	336	670
Dandara (2015)[53]	Literature	Cape Town	1977-2007	2	1.84	1092	593	1685
Swaziland								
IARC (2003)	CIA	Manzini	1996-1999	1	3.33	106 (14.0)	38 (4.1)	144
Total cases (Southern Africa)						***10874***	***6111***	***16985***
			Middle Africa					
Congo								
IARC (2003)	CIA	Brazzaville	1996-1999	1	1.57	4 (0.5)	1 (0.1)	5
IARC (In press)	CIA	Brazzaville	2009-2013	1	1.58	7 (0.5)	2 (0.1)	9
Total cases (Middle Africa)						***11***	***3***	***14***
			Western Africa					
Burkina Faso								
IARC (2003)	CIA	Ouagadougou	1998	1	1.08	5	4	9
Cote d'Ivoire								
Echimane (2000)[54]	Literature	Abidjan	1995-1997	1	9.00	9 (0.7)	1 (0.2)	10
IARC (In press)	CIA	Abidjan	2012-2013	1	0.81	3 (0.2)	3 (0.3)	6
Ghana								
Tettey (2012)[55]	Literature	Accra	1992-2010	2	4.07	122	30	152
IARC (In press)	CIA	Kumasi	2012-2013	1	1.06	1 (0.1)	2 (0.2)	3
Guinea								
IARC (2003)	CIA	Conakry	1996-1999	1	2.10	13 (0.9)	5 (0.5)	18
IARC (In press)	CIA	Conakry	2001-2010	1	1.92	13 (0.8)	3 (0.1)	16
Mali								
IARC (1997)	CI5 (vol. VII)	Bamako	1988-1992	1	0.99	12 (1.5)	7 (0.8)	19
IARC (2002)	CI5 (vol. VIII)	Bamako	1994-1996	1	1.17	17 (3.0)	9 (1.7)	26
Niger								
IARC (2003)	CIA	Niamey	1993-1999	1	0.94	7 (1.0)	7 (1.3)	14
IARC (In press)	CIA	Niamey	2006-2009	1	2.08	13 (1.2)	2 (0.2)	15

Nigeria								
Awojobi (1996)	Literature	Eruwa, Oyo state	1986-1995	1	0.83	5	6	11
Ojo (1996)	Literature	Ife-Ijesha	1993-1995	1	1.00	2	2	4
Adegboye (2002)[56]	Literature	Ibadan	1986-1996	2	2.10	21	10	31
IARC (2003)	CIA	Ibadan	1998-1999	1	2.31	7 (1.1)	2 (0.3)	9
IARC (In press)	CIA	Ibadan	2006-2009	1	1.93	15 (1.0)	7 (0.4)	22
The Gambia								
IARC (2002)	CI5 (vol. VIII)		1997-1998	1	1.27	6 (1.4)	3 (1.1)	9
IARC (In press)	CIA		2007-2011	1	2.15	22 (1.0)	8 (0.5)	30
Togo								
Amegbor (2008)[57]	Literature	Lome	1986-2005	2	2.25	72	32	104
Total cases (Western Africa)						***365***	***143***	***508***
Total cases						***17096***	***9838***	***26934***

A male excess of EC was observed for the majority of countries investigated, including the high incidence regions of Eastern and Southern Africa, where a significant male excess predominated. Estimated regional ratios were 1.6 (95% CI: 1.4, 1.8) and 1.8 (95% CI: 1.5, 2.0) for Eastern and Southern Africa, respectively. The countries with the highest male excesses were Tanzania in Eastern Africa (2.3; 95% CI: 1.9, 2.6) and Swaziland in Southern Africa (3.3; 95% CI: 2.3, 4.8), which was based on 1996-1999 incidence data from the Swaziland Cancer Registry published in *Cancer in Africa* [14]. In contrast, a significant female excess was only observed in Sudan (0.5; 95% CI: 0.4, 0.6) and is based solely on regional (not country-wide) case series data from a single study [19]. The absence of a significant male excess was observed for two other Eastern African countries: Mozambique (1.4; 95% CI: 0.7, 2.8) and Ethiopia (1.2; 95% CI: 0.7, 2.0). Estimates for several countries, mostly in the low incidence region, were based on a limited number of cases. This was particularly the case for Burkina Faso (9 cases), Congo (14 cases) and Cote d'Ivoire (16 cases).

The above country-specific summaries mask a large degree of heterogeneity, demonstrated by the I^2 estimates in Figure 3, particularly for Ethiopia, Kenya, Uganda, Zimbabwe, South Africa, Ghana and Cote d'Ivoire. Country-specific estimates are also mapped in Figure 4 and visual examination of the map shows no obvious spatial trends.

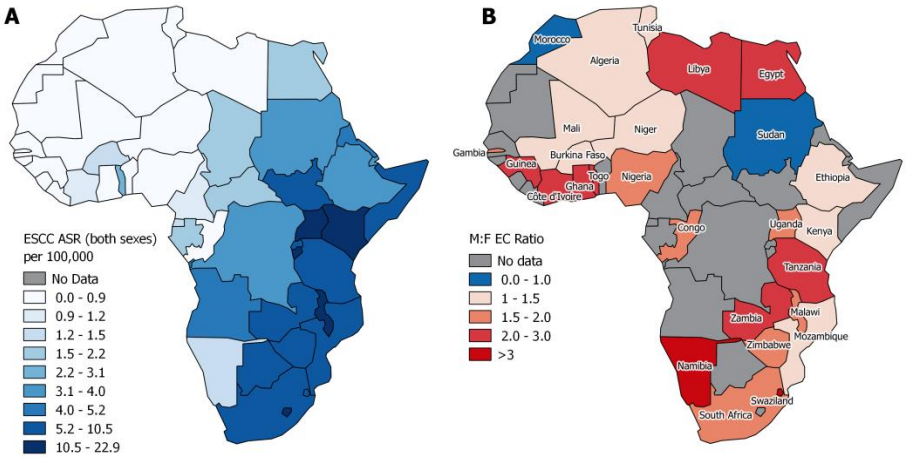

Figure 4 (A) Country-specific estimated age-standardized incidence rates of esophageal squamous cell carcinoma (Arnold et al. 2014) and (B) country-specific sex ratios of esophageal cancer estimated in the present study.

3.4 Age-specific EC sex ratios

Age-specific sex ratios are shown in Figure 5 and were grouped by region, with the exception of Ethiopia, which was displayed separately due to the lack of evidence of a male excess found for this country. For the Eastern and Southern African high incidence regions, there was evidence (although not significant) of a male excess (M:F 1.3 and 1.4) as early as age 20-29 years in both regions. The 20-29 year age group estimate for Eastern Africa has a large contribution from a focussed study of <30 year olds (n=109, M:F=1.48) in West Kenya [11]. The excess was lower and non-significant when this study was omitted (1.2; 95% CI: 0.8, 1.7), but was already present in Eastern Africa (M:F = 1.8) in 30-39 year olds. A greater degree of heterogeneity was observed between estimates for older age groups in the Eastern and Southern African high incidence regions and Ethiopia. Conversely, there was no heterogeneity in the low incidence region, a male excess was only apparent in ages 40 and over.

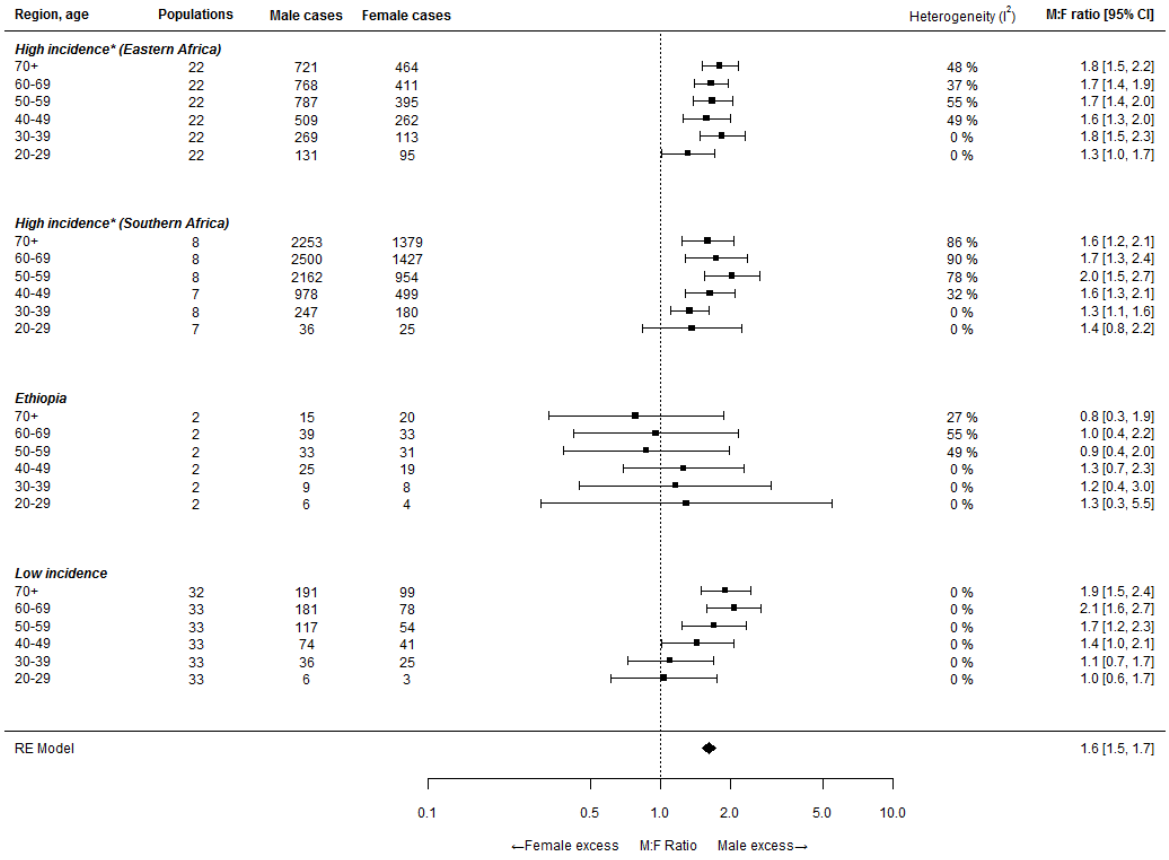

Figure 5 Forest plot of age-specific sex ratios grouped by region. Estimates were made using random effects models. *High incidence denotes countries for which the male or female EC ASR exceeds the global mean in GLOBOCAN.

3.5 Sources of heterogeneity

To investigate whether data source differences explained the heterogeneity within country-specific sex ratios, country-specific estimates were calculated using registry (both CI5 and CIA) and literature data separately. Countries with notably high (I-squared >60%) heterogeneities, from which sufficient data were available from both registry and literature sources (Uganda, Kenya, Ethiopia, South Africa) did not show a marked reduction in heterogeneity. For example, in Uganda, the sex ratio estimates were 1.7 and 1.9 for registry and literature data, respectively (1.8 combined) with I-squared values of 74% and 80% (78% combined).

Upon further investigation by location within country (estimates provided here and not in tables), although Kenya had a smaller relative male excess (M:F 1.4) than other high incidence East African countries (M:F of 1.8-2.3), heterogeneity was explained by location: estimates from the capital Nairobi were nearer 1 (M:F 1.0 (0.9, 1.2), I^2=0%), whilst the combined ratio elsewhere, largely studies in Bomet and West Kenya, was 1.6 (1.4, 1.8), I^2=0%. Similarly in Uganda, the capital had a smaller relative male excess (M:F 1.5 (1.3-1.8) I^2=53%) than other areas of the country (M:F 3.5 (2.4, 4.9), I^2=0%). In South Africa, national data provided the highest ratio (M:F 2.5) and the Eastern Cape/Transkei area the lowest (1.3 (1.0-1.6)) . Furthermore, when restricted to count ratios alone, estimates may have been more susceptible to spatial variation if population sex imbalances were present. We were able to observe this for one study [53], reporting on a rural population in South Africa with a dominant female population above age 20. Age-specific EC counts were reported without corresponding population denominators, but an overall ASR was also reported. The age-adjusted sex ratio generated using EC counts was 0.93, but increased to 1.62 when the ratio was calculated using the ratio of ASRs.

4. Discussion

This study is the first to systematically review and report sex ratios of EC incidence in Africa and does so for 27 countries. The principal findings were (i) a decrease in male-to-female ratios over time; (ii) an overall male excess in EC incidence across Africa of between 1.4 and 2 fold; (iii) a high degree of heterogeneity both between and within country-specific estimates and (iv) in high incidence countries where young cases occur, a male excess already evident in 30-39 year olds.

The study was hindered by a comparatively low quantity of high quality cancer incidence data in African countries, namely due to the lack of established, population based cancer registries on the continent. Sex differentials in EC incidence rates can be estimated using GLOBOCAN, but their validity is undermined by the fact that many incidence rates, in the absence of high quality population based registry data, are based on those from neighbouring countries [1]; only 2% of the continent's population was included in the last volume of CI5 [58]. Many of the country-specific estimates reported in this paper are based on data from a single site or region and do not represent the country as a whole – e.g. Zimbabwe, for which data were exclusively from the capital city of Harare. However, the situation is improving, and the wealth of new data from the CISSA series, in addition to the few registries already reported in CI5 and CIA, enabled a meaningful analysis that was sufficient to investigate EC sex ratio by time, geography and age. In many instances, we relied on count ratios to estimate rate ratios of EC. While we demonstrated that count ratios generally agreed with rate ratios (Figure S1), exceptions may occur in populations with an uneven underlying sex distribution. The two most extreme examples that we observed were an almost two-fold increase in a male excess (3.68 to 6.62) in the predominantly male population of Harare, Zimbabwe and the disappearance of a male excess (1.62 to 0.89) in the predominantly female population of the Eastern Cape province of South Africa. These are the farthest points above and below the line in Figure S1, respectively.

Comparisons between estimates derived in the present paper and worldwide estimates are shown in Figure 6. Figure 6 (A) shows a decrease in sex ratios with increasing incidence in women (used here as an indicator of underlying incidence in the general population). For populations with very high EC incidence (ASR_F>20), sex ratios in Africa (1.5 to 2) are comparable to those from Chinese registries, and these exceed those from Iran (1.23). For populations with medium EC incidence (ASR_F 5-20), sex ratios in a few African countries (e.g. Tanzania, Zambia) are higher than ratios from other registries, mostly in India, with comparable rates. Figure 6 (B) demonstrates that, although the male excess is much lower in higher incidence countries on a relative scale, the absolute difference in rates between men and women increases sharply with increasing underlying incidence.

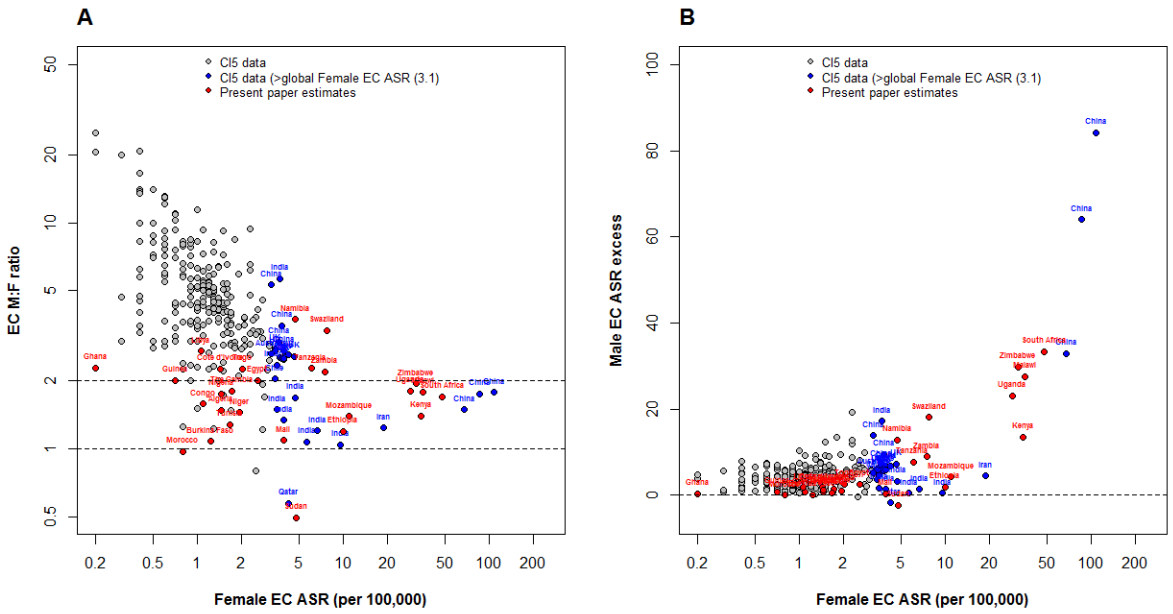

Figure 6 Male-to-female EC ratios plotted against EC ASR in women. Global data (excluding Africa) from CI5 is plotted in comparison to African estimates from the present study. CI5 data are plotted by individual registry and labelled by country.

The substantial decline that we observed in sex ratios over time could be attributed to a number of factors. While etiological insights are of primary interest, gender inequalities in healthcare access giving rise to referral biases, may also affect sex-differentials in incidence in the African setting [58,59]. There is some indication of this in sub-Saharan Africa, with present-day male referral bias having been reported in children [60] and middle-aged women [61] as well as historical reports of barriers faced by elderly women in rural areas [62]. Such referral biases would be expected to affect other cancer sites too, but we are not aware of any studies examining this issue. Exposure profiles may also have changed with time. Whatever the underlying reason for much higher earlier EC male excesses, it was necessary to exclude earlier data as they did not represent the present day scenario. While there were no obvious spatial trends in sex ratios, the large degree of heterogeneity among country-specific estimates, which persisted after stratifying by data source, suggests that risk profiles differ on a short spatial scale within countries. This is not unexpected given the large spatial variation in EC rates, both in Africa and other high incidence areas.

In respect of the putative risk factors for ESCC – tobacco, alcohol, hot beverages, environmental chemical exposures (PAHs, nitrosamines and mycotoxins) and micronutrient

deficiencies – tobacco and alcohol consumption are both more prevalent among African males [63,64], although the under-reporting of illicit home brew consumption [65] limits the interpretive value of alcohol statistics. It is likely that PAH exposures are higher for females due to time spent cooking indoors with poor ventilation [66]. Elucidating the gender differences between specific risk factors will form a component of ongoing etiologic research. While a male excess was evident, an abnormally high incidence rates among females exists in African high incidence countries. This generates two possible hypotheses to be tested in future: (1) that male-patterned exposures are exacerbating the effects of an underlying, more ubiquitous factor or, alternatively (2) that independent, female-specific exposures are prevalent, but are less potent than those found in men. Countries, such as Sudan and Ethiopia, where a statistically significant male excess was not observed, may offer unique opportunities to test these hypotheses.

Further, the presence of the male excess from early ages (30s) particularly in Eastern Africa, is intriguing. When compared to other upper aerodigestive or respiratory cancers in selected populations (US SEER white and black, Scotland, Calvados), although extremely rare, M:F lung cancer IRRs are 1.2 in US Whites in the 30s, and 2 in Scotland. In the 30s, EC almost never occurs, but for oral cavity and pharynx, male excesses are already present (1.5 Scotland, 1.6 US White, 2.0 US Black, 8.3 Calvados). Thus, observing such a young male excess in East Africa may not be implausible, though the drivers of any young ECs are unknown. A male excess, if not due to gender referral biases, must at least partially be driven by environmental agents acting from early in the life-course, or particularly potent ones, in addition to inherited susceptibility. For the latter, family history of EC has been reported as a risk factor with a high prevalence in some studies[11] but not all.

The presence of a non-negligible male excess in many of the high EC incidence countries of Southern and Eastern Africa points towards a potentially large preventable burden of disease. First, epidemiologic studies should be able to identify factors that contribute to the male excess, as exposure heterogeneity must be present. At M:F ratios of 1.5 and 2 respectively, if male incidence rates could be reduced to those in females, 20% and 33% of all EC cases, and 33% and 50% of male EC cases would be prevented. Whatever the root causes of high incidence rates of EC in Eastern and Southern Africa, these findings suggest that a large fraction of the disease burden could be prevented by targeting male patterned, modifiable risk factors.

Acknowledgements

The authors are grateful to Dr Max Parkin for sharing advice regarding the manuscript.

Funding

The work reported was undertaken during the tenure of a Postdoctoral Fellowship from the International agency for Research on cancer, partially supported by the European Commission FP7 Marie Curie Actions – People – Co-funding of regional, national and international programmes (COFUND).

References

1 Ferlay, J. *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J. Cancer* **136**, E359-E386 (2015).
2 Arnold, M., Soerjomataram, I., Ferlay, J. & Forman, D. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* **64**, 387 (2015).
3 Schaafsma, T. *et al.* Africa's Oesophageal Cancer Corridor: Geographic variations in incidence correlate with certain micronutrient deficiencies. *PLoS. One* (2015).
4 Chasimpha, S. J., Parkin, D. M., Masamba, L. & Dzamalala, C. P. Three year cancer incidence in Blantyre, Malawi (2008-2010). *International Journal of Cancer* (2017).
5 McCormack, V. A. *et al.* Informing etiologic research priorities for squamous cell esophageal cancer in Africa: A review of setting-specific exposures to known and putative risk factors. *International Journal of Cancer* (2016).
6 Kamangar, F., Chow, W. H., Abnet, C. C. & Dawsey, S. M. Environmental causes of esophageal cancer. *Gastroenterol. Clin North Am* **38**, 27-57 (2009).
7 Ly, D., Forman, D., Ferlay, J., Brinton, L. A. & Cook, M. B. An international comparison of male and female breast cancer incidence rates. *International journal of cancer* **132**, 1918-1926 (2013).
8 Devesa, S. S., Bray, F., Vizcaino, A. P. & Parkin, D. M. International lung cancer trends by histologic type: male: female differences diminishing and adenocarcinoma rates rising. *International journal of cancer* **117**, 294-299 (2005).
9 Rahbari, R., Zhang, L. & Kebebew, E. Thyroid cancer gender disparity. *Future Oncology* **6**, 1771-1779 (2010).
10 Pampel, F. Tobacco use in sub-Sahara Africa: estimates from the demographic health surveys. *Social science & medicine* **66**, 1772-1783 (2008).
11 Dawsey, S. P. *et al.* Esophageal cancer in young people: a case series of 109 cases and review of the literature. *PLoS. One* **5**, e14080 (2010).
12 Phillips, S. P. Defining and measuring gender: A social determinant of health whose time has come. *International Journal for Equity in Health* **4**, 11 (2005).
13 IARC. Cancer Incidence in Five Continents. Volumes I-X. Online Resource. Available: http://ci5.iarc.fr/Default.aspx. (2017).
14 Parkin, D. *et al.* Cancer in Africa. *Epidemiology and prevention. Lyon: IARC Press* (2003).
15 RCoreTeam. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/. (2016).
16 Gelfand, M. Health care for Africans in Rhodesia. *Central African Journal of Medicine* **22**, 252-257 (1976).

17 Bahnassy, A. A., Zekri, A. R. N., Abdallah, S., El-Shehaby, A. M. & Sherif, G. M. Human papillomavirus infection in Egyptian esophageal carcinoma: Correlation with p53, p21waf, mdm2, C-erbB2 and impact on survival. *Pathology international* **55**, 53-62 (2005).
18 Chbani, L., Hafid, I., Berraho, M., Nejjari, C. & Amarti, A. Digestive cancers in Morocco: Fez-Boulemane region. *Pan African Medical Journal* **13** (2012).
19 Gasmelseed, N. *et al.* Patterns of Esophageal Cancer in the National Cancer Institute at the University of Gezira, in Gezira State, Sudan, in 1999-2012. *Asian Pacific Journal of Cancer Prevention* **16**, 6481-6490 (2015).
20 Ali, A., Ersumo, T. & Johnson, O. Oesophageal carcinoma in Tikur Anbessa Hospital, Addis Ababa. *East Afr. Med. J* **75**, 590-593 (1998).
21 Ashine, S. & Lemma, B. Malignant tumours at Yirga Alem Hospital. *Ethiopian medical journal* **37**, 163-172 (1999).
22 Shewaye, A. & Seme, A. Risk factors associated with oesophageal malignancy among Ethiopian patients: a case control study. *East and Central African Journal of Surgery* **21**, 33-39 (2016).
23 Leon, M. E. *et al.* Qat use and esophageal cancer in Ethiopia: A pilot case-control study. *PloS one* **12**, e0178911 (2017).
24 White, R. E., Abnet, C. C., Mungatana, C. K. & Dawsey, S. M. Oesophageal cancer: a common malignancy in young people of Bomet District, Kenya. *Lancet* **360**, 462-463 (2002).
25 Lodenyo, H. *et al.* Patterns of upper gastrointestinal diseases based on endoscopy in the period 1998-2001. *African journal of health sciences* **12**, 49-54 (2005).
26 Ogendo, S. Weight change post oesophagectomy for carcinoma of oesophagus. *East African medical journal* **84**, 271-278 (2007).
27 Parker, R. K. *et al.* Stents for proximal esophageal cancer: a case-control study. *Gastrointest. Endosc* **73**, 1098-1105 (2011).
28 Patel, K., Wakhisi, J., Mining, S., Mwangi, A. & Patel, R. Esophageal Cancer, the Topmost Cancer at MTRH in the Rift Valley, Kenya, and Its Potential Risk Factors. *ISRN. Oncol* **2013**, 503249 (2013).
29 Banda, L. T., Parkin, D. M., Dzamalala, C. P. & Liomba, N. G. Cancer incidence in Blantyre, Malawi 1994-1998. *Trop. Med. Int Health* **6**, 296-304 (2001).
30 Crofts, T. A tale of two cities–oesophageal cancer in Malawi and Scotland. *Malawi Medical Journal* **20**, 135-139 (2008).
31 Mothes, H. *et al.* Do patients in rural Malawi benefit from upper gastrointestinal endoscopy? *Tropical doctor* **39**, 73-76 (2009).
32 Gyorki, D. E., Muyco, A., Kushner, A. L., Brennan, M. F. & Kingham, T. P. Cancer surgery in low-income countries: an unmet need. *Archives of Surgery* **147**, 1135-1140 (2012).
33 Wolf, L. L. *et al.* Esophagogastroduodenoscopy in a public referral hospital in Lilongwe, Malawi: spectrum of disease and associated risk factors. *World J. Surg* **36**, 1074-1082 (2012).
34 Mtonga, P. *et al.* Biopsy case mix and diagnostic yield at a Malawian central hospital. *Malawi Medical Journal* **25**, 62-64 (2013).
35 Mlombe, Y. B. *et al.* Environmental risk factors for oesophageal cancer in Malawi: A case-control study. *Malawi. Med. J* **27**, 88-92 (2015).
36 Mchembe, M. D. *et al.* Endoscopic and clinicopathological patterns of esophageal cancer in Tanzania: experiences from two tertiary health institutions. *World journal of surgical oncology* **11**, 257 (2013).
37 Gabel, J. V. *et al.* Clinical and epidemiologic variations of esophageal cancer in Tanzania. *World journal of gastrointestinal oncology* **8**, 314 (2016).
38 Alema, O. N. & Iva, B. Cancer of the esophagus: histopathological sub-types in northern Uganda. *Afr. Health Sci* **14**, 17-21, doi:10.4314/ahs.v14i1.4 [doi];jAFHS.v14.i1.pg17 [pii] (2014).

39 Okello, S. *et al.* Population attributable fraction of Esophageal squamous cell carcinoma due to smoking and alcohol in Uganda. *BMC cancer* **16**, 446 (2016).
40 Kayamba, V. *et al.* HIV infection and domestic smoke exposure, but not human papillomavirus, are risk factors for esophageal squamous cell carcinoma in Zambia: a case-control study. *Cancer Med* **4**, 588-595, doi:10.1002/cam4.434 [doi] (2015).
41 Asombang, A. W. *et al.* Esophageal squamous cell cancer in a highly endemic region. *World journal of gastroenterology* **22**, 2811 (2016).
42 Levy, R., Oosthuizen, M., Degiannis, E. & Lambrechts, H. Elevated reversible and irreversible lipid peroxidation in human oesophageal cancer. *Anticancer research* **18**, 1325-1328 (1998).
43 Dietzsch, E. & Parker, M. I. Infrequent somatic deletion of the 5'region of the COL1A2 gene in oesophageal squamous cell cancer patients. *Clinical chemistry and laboratory medicine* **40**, 941-945 (2002).
44 Pacella-Norman, R. *et al.* Risk factors for oesophageal, lung, oral and laryngeal cancers in black South Africans. *Br. J. Cancer* **86**, 1751-1756 (2002).
45 Dlamini, Z. & Bhoola, K. Esophageal cancer in African blacks of Kwazulu Natal, South Africa: an epidemiological brief. *Ethn. Dis* **15**, 786-789 (2005).
46 Dandara, C., Li, D. P., Walther, G. & Parker, M. I. Gene-environment interaction: the role of SULT1A1 and CYP3A5 polymorphisms as risk modifiers for squamous cell carcinoma of the oesophagus. *Carcinogenesis* **27**, 791-797, doi:10.1093/carcin/bgi257 (2006).
47 Matsha, T. *et al.* Traditional home-brewed beer consumption and iron status in patients with esophageal cancer and healthy control subjects from Transkei, South Africa. *Nutrition and cancer* **56**, 67-73 (2006).
48 Li, D.-P., Dandara, C., Walther, G. & Parker, M. I. Genetic polymorphisms of alcohol metabolising enzymes: their role in susceptibility to oesophageal cancer. *Clinical Chemical Laboratory Medicine* **46**, 323-328 (2008).
49 Van der Merwe, T. *et al.* Epidemiological changes in oesophageal cancer at National Hospital, Bloemfontein: 1995, 2000 and 2005. *African Journal of Primary Health Care and Family Medicine* **2**, 1-5 (2010).
50 Somdyala, N. I., Bradshaw, D., Gelderblom, W. C. & Parkin, D. M. Cancer incidence in a rural population of South Africa, 1998–2002. *International Journal of Cancer* **127**, 2420-2429 (2010).
51 Sitas, F. *et al.* The spectrum of HIV-1 related cancers in South Africa. *Int J. Cancer* **88**, 489-492 (2000).
52 Sewram, V., Sitas, F., O'Connell, D. & Myers, J. Diet and esophageal cancer risk in the Eastern Cape Province of South Africa. *Nutr. Cancer* **66**, 791-799, doi:10.1080/01635581.2014.916321 [doi] (2014).
53 Dandara, C., Robertson, B., Dzobo, K., Moodley, L. & Parker, M. I. Patient and tumour characteristics as prognostic markers for oesophageal cancer: a retrospective analysis of a cohort of patients at Groote Schuur Hospital. *European Journal of Cardio-Thoracic Surgery* **49**, 629-634 (2015).
54 Echimane, A. K. *et al.* Cancer incidence in Abidjan, Ivory Coast. *Cancer* **89**, 653-663 (2000).
55 Tettey, M. *et al.* The changing epidemiology of esophageal cancer in sub-Saharan Africa–the case of Ghana. *Pan African Medical Journal* **13** (2012).
56 Adegboye, V., Obajimi, M., Ogunseyinde, A., Brimmo, I. & Adebo, A. Trans-hiatal oesophagectomy as a palliative treatment for carcinoma of the oesophagus. *East African medical journal* **79**, 311-316 (2002).
57 Amegbor, K., Napo-Koura, G., Songne-Gnamkoulamba, B., Redah, D. & Tekou, A. Epidemiological and pathological aspects of gastrointestinal tumors in Togo. *Gastroentérologie Clinique et Biologique* **32**, 430-434 (2008).
58 Klasen, S. Nutrition, health and mortality in sub-Saharan Africa: Is there a gender bias? (1996).

59 Chirowa, F., Atwood, S. & Van der Putten, M. Gender inequality, health expenditure and maternal mortality in sub-Saharan Africa: A secondary data analysis. *African Journal of Primary Health Care and Family Medicine* **5**, 1-5 (2013).

60 Rockers, P. C. & McConnell, M. Child Gender and Parental Reporting of Illness Symptoms in Sub-Saharan Africa. *The American Journal of Tropical Medicine and Hygiene* **96**, 994-1000 (2017).

61 Ibanez-Gonzalez, D. L. & Norris, S. A. Chronic non-communicable disease and healthcare access in middle-aged and older women living in Soweto, South Africa. *PloS one* **8**, e78800 (2013).

62 Skinner, M. E. Malignant disease of the gastrointestinal tract in the Rhodesian African, with special reference to the urban population of Bulawayo. A preliminary report. *Natl. Cancer Inst. Monogr* **25**, 57-71 (1967).

63 Sreeramareddy, C. T., Pradhan, P. M. & Sin, S. Prevalence, distribution, and social determinants of tobacco use in 30 sub-Saharan African countries. *BMC. Med* **12**, 243, doi:10.1186/s12916-014-0243-x [doi];s12916-014-0243-x [pii] (2014).

64 (GISAH), G. I. S. o. A. a. H. *Global Health Observatory Data Repository,World Health Organization 2014* (2014). <http://apps.who.int/gho/data/node.main.A1036?lang=en&showonly=GISAH>.

65 Papas, R. K. *et al.* Estimating alcohol content of traditional brew in Western Kenya using culturally relevant methods: the case for cost over volume. *AIDS Behav* **14**, 836-844 (2010).

66 Titcombe, M. E. & Simcik, M. Personal and indoor exposure to PM(2).(5) and polycyclic aromatic hydrocarbons in the southern highlands of Tanzania: a pilot-scale study. *Environ. Monit. Assess* **180**, 461-476 (2011).